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Cardiovascular pressure-volume loops

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Keywords: cardiovascular pressure-volume loops, ventricular performance, cardiac cycle

Introduction

Pressure-volume (PV) loops are a modality used to depict the relationship between pressure and volume in the ventricle.[1] They are used to represent ventricular performance during a cardiac cycle. A loop is drawn for a single cardiac cycle that is divided into four primary phases. The four phases are ventricular filling (diastole), isovolumetric contraction (systole), ejection (systole), and isovolumetric relaxation (diastole).

Acquiring PV measurements

PV loops are mostly performed in animal studies.[2] A PV catheter is inserted into the ventricle being studied. This is achieved either through the carotid/aorta in a closed chest or the ventricle in an open chest (Figure 1). Changes in volume, pressure, and inotropy are simulated as measurements are taken.

Figure 1: Aortic approach of the PV catheter[1]

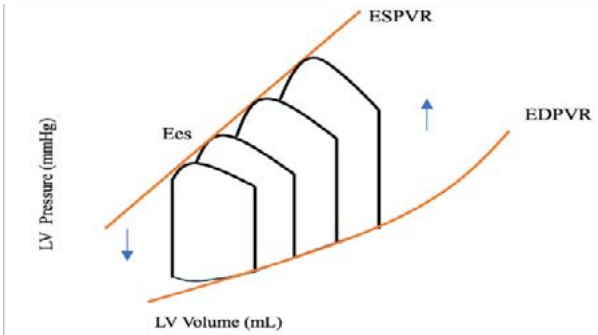


Figure 2: Illustration of simulated preload conditions concerning pressure and SV
*LV - left ventricle, Ees - end-systolic elastance, ESPVR - end-systolic pressure volume relationship, EDPVR - end-diastolic pressure volume relationship

An example of volume simulation is achieved with the manipulation of the inferior vena cava to change the loading conditions to simulate different preload scenarios (Figure 2). The haemodynamic and physiological events that can be derived from these loops include stroke volume (SV), cardiac output, ejection fraction, and myocardial contractility.

Characteristics of a PV loop (Figure 3)

The PV loop depicts four phases:

1. Phase a – ventricular filling (diastole)
2. Phase b – isovolumetric contraction (systole)
3. Phase c – ejection (systole)
4. Phase d – isovolumetric relaxation (diastole)

Phase a

Phase a is characterised by the mitral valve opening and the filling of the ventricle. This phase is preceded by a phase where the left ventricular (LV) pressure drops significantly below the volume of the full left atrium. The volume in the LV at the beginning of the phase is termed end-systolic volume (ESV). The volume in the LV increases, accompanied by a gradual increase in pressure as the ventricle fills up. This phase ends with a full ventricle with a higher pressure than in the atrium. The mitral valve, therefore closes. The volume in the LV at this point is termed end-diastolic volume (EDV). The difference between the EDV and the ESV determines the SV. This phase is termed diastole.[3,4]

Phase b

Phase b begins with a full LV and closed mitral and aortic valves. The LV then generates pressure against both closed valves while the volume remains the same (isovolumetric contraction), aimed at exceeding the pressure in the aorta to generate flow. The end of this phase occurs when the aortic valve opens.[3,4]

Phase c

Phase c begins when the aortic valve opens, and flow through the aortic valve starts while the ventricle continues to generate pressure to a peak ventricular pressure before it begins to relax. This phase is termed systole.[3,4]

Phase d

Phase d begins with the closure of the aorta whilst the mitral valve remains open with a constant volume (isovolumetric relaxation). The LV continues to relax until the LV pressure is below the left atrial pressure for phase a to begin again.[3,4]

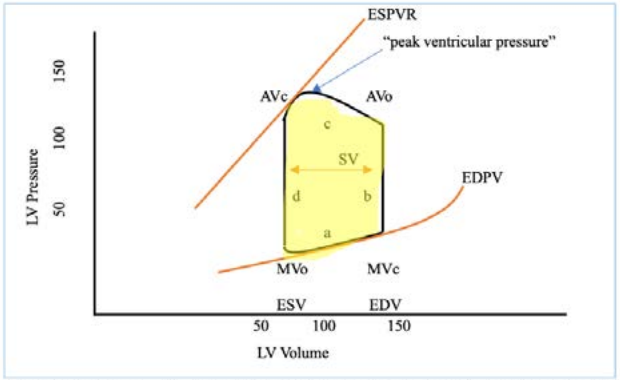


Figure 3: Characteristics of the PV loop
*LV - left ventricle, Ees - end-systolic elastance, ESPVR – end-systolic pressure-volume relationship, EDPVR – end-diastolic pressure-volume relationship, AVc – aortic valve closure, Avo - aortic valve opening, MVo – mitral valve opening, MVc – mitral valve closure, ESV – end-systolic volume, EDV – end-diastolic volume, SV – stroke volume, phases a,b,c,d – ventricular filling /diastole, isovolumetric contraction/systole, ejection/systole, and isovolumetric relaxation/diastole.

The pressure and volume measurements are performed directly at the catheter as load-independent parameters. Pressures are plotted on the y-axis, and volumes are on the x-axis. The following parameters can be determined from the measurements:[2,3]

- SV – the volume of blood pumped from the left ventricle per beat (SV = EDV - ESV).
- Stroke work (SW) – work performed to eject a volume of blood [SW = SV × mean arterial pressure (MAP)], the yellow area on the graph.
- **End-diastolic pressure-volume relationship (EDPVR) slope** – ventricular compliance.
- **End-systolic pressure-volume relationship (ESPVR) slope** – ventricular inotrope.
- End-systolic elastance (Ees) – compliance/cardiac contractility.

Valve pathology and PV loops

Mitral stenosis (Figure 4)

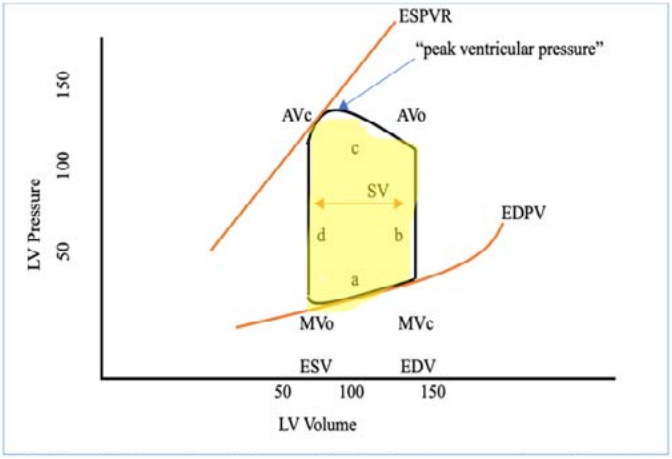
Stenosis of the mitral valve presents a mechanical obstruction to the filling of the LV. The effect is reduced preload (red loop), represented by a decrease in EDV. The lower EDV leads to a lower ventricular filling pressure left ventricular end-diastolic pressure (LVEDP).[2]

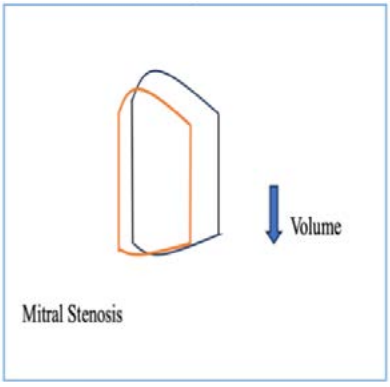
The heart contractility is, therefore reduced through the intrinsic Frank-Starling mechanism leading to lower peak ventricular pressure. Therefore, there is a lower ESV, however not enough to offset the reduction in EDV and consequent lower SV. Ventricular SW is also reduced.[5]

Mitral regurgitation (Figure 5)

Mitral regurgitation is characterised by losses in both true isovolumetric contraction and relaxation. This leads to the loss of phases b and d in the PV loop. The ESV is reduced to flow back into the atrium during isovolumetric relaxation, and the EDV is increased due to unregulated excessive flow from the atrium during diastolic filling.[6]

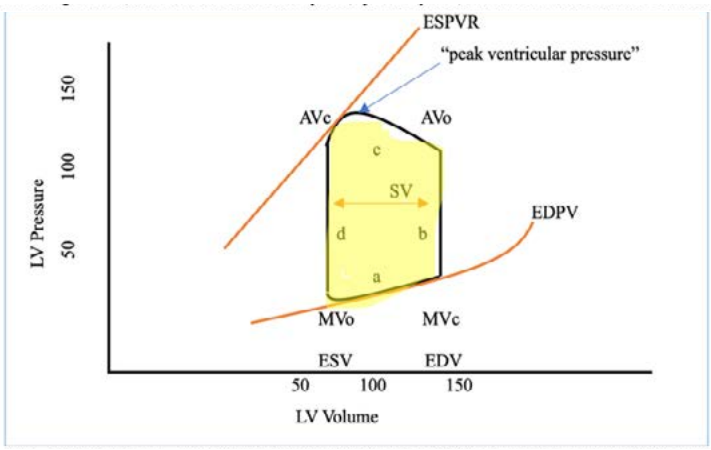
This leads to increased LVEDP, SV, and SW. The ventricle cannot generate an adequate peak pressure and, therefore, ejection into the aorta is reduced.

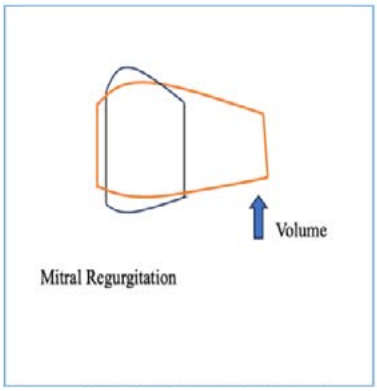




Decreased ESV, EDV, SV, SW

Figure 4: Mitral stenosis
*LV - left ventricle, Ees - end-systolic elastance, ESPVR – end-systolic pressure-volume relationship, EDPVR – end-diastolic pressure-volume relationship, AVc – aortic valve closure, Avo - aortic valve opening, MVo – mitral valve closure, MVc – mitral valve closure, ESV – end-systolic volume, EDV – end-diastolic volume, SV – stoke volume, phases a,b,c,d – ventricular filling /diastole, isovolumetric contraction/systole, ejection/systole, and isovolumetric relaxation/diastole.

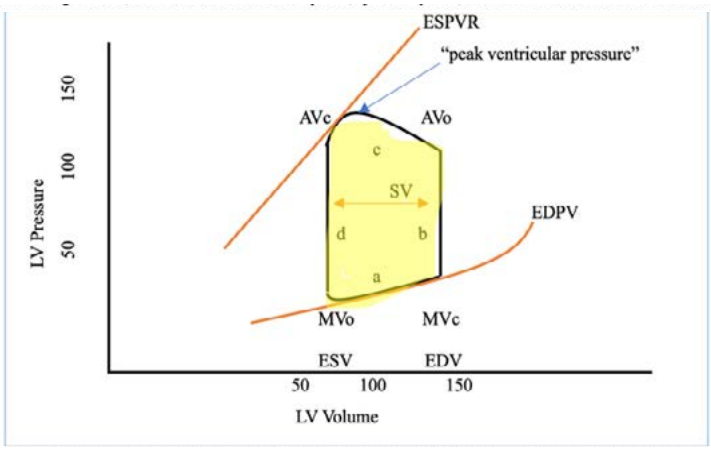


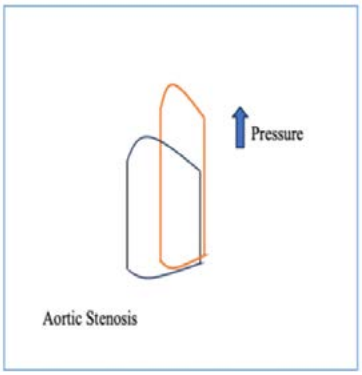


Increased LVEDP, SW, SV, EDV. Reduced ESV.

Figure 5: Mitral regurgitation

*LV - left ventricle, Ees - end-systolic elastance, ESPVR – end-systolic pressure volume relationship, EDPVR – end-diastolic pressure volume relationship, AVc – aortic valve closure, Avo - aortic valve opening, MVo – mitral valve opening, MVc – mitral valve closure, ESV – end-systolic volume, EDV – end-diastolic volume, SV – stoke volume, phases a,b,c,d – ventricular filling /diastole, isovolumetric contraction/systole, ejection/systole, and isovolumetric relaxation/diastole.

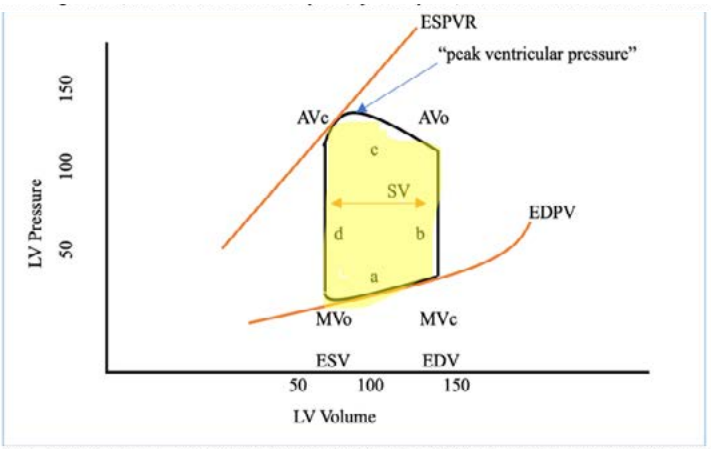


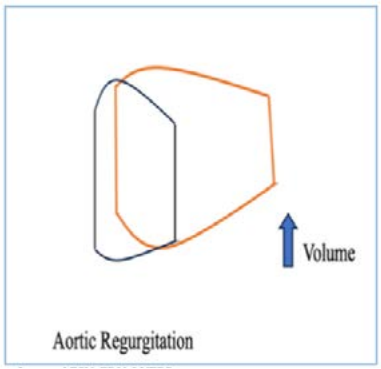


Increase in EDV, peak pressure, decreased SV.

Figure 6: Aortic stenosis

*LV - left ventricle, Ees - end-systolic elastance, ESPVR – end-systolic pressure volume relationship, EDPVR – end-diastolic pressure volume relationship, AVc – aortic valve closure, Avo - aortic valve opening, MVo – mitral valve opening, MVc – mitral valve closure, ESV – end-systolic volume, EDV – end-diastolic volume, SV – stoke volume, phases a,b,c,d – ventricular filling /diastole, isovolumetric contraction/systole, ejection/systole, and isovolumetric relaxation/diastole.





Increased ESV, EDV, LVEDP.

Figure 7: Aortic Regurgitation

*LV - left ventricle, Ees - end-systolic elastance, ESPVR – end-systolic pressure volume relationship, EDPVR – end-diastolic pressure volume relationship, AVc – aortic valve closure, Avo - aortic valve opening, MVo – mitral valve opening, MVc – mitral valve closure, ESV – end-systolic volume, EDV – end-diastolic volume, SV – stoke volume, phases a,b,c,d – ventricular filling /diastole, isovolumetric contraction/systole, ejection/systole, and isovolumetric relaxation/diastole.

Aortic stenosis (Figure 6)

Aortic stenosis presents a mechanical obstruction to ventricular outflow. The ventricle has to generate a very high peak pressure to overcome this pressure for ejection (phase c). An inadequate volume is ejected with residual volume at the end of systole, represented as a high ESV.

During diastole, there is an elevation in preload due to volume incoming from the atrium added to the increased ESV. This leads to an increase in EDV. An increased EDV requires the ventricle to generate very high pressures during isovolumetric contraction following the Frank-Starling mechanism to eject SV. There is, however, still a reduction in SV in the face of an increase in SW.[7]

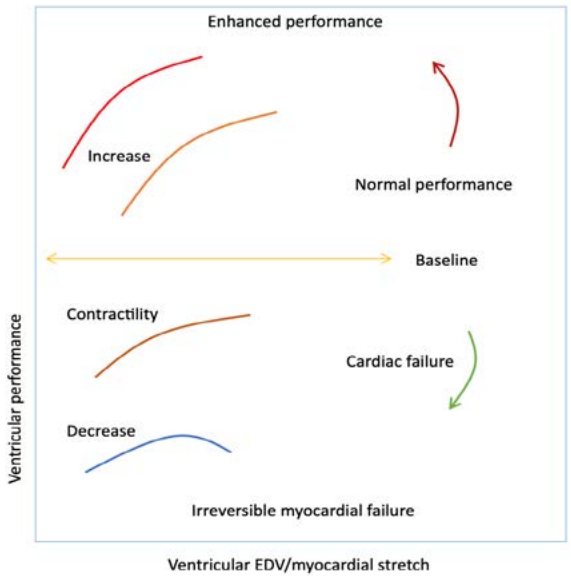


Figure 8: Ventricular performance

Aortic regurgitation (Figure 7)

Aortic regurgitation is characterised by the failure to close during both isovolumetric contraction and relaxation. The ventricle starts filling up during isovolumetric relaxation before the mitral valve opens.

This leads to an increase in ESV. During true diastolic filling, the ventricle continues to fill up from two sources, the mitral and aortic valves, leading to an increase in EDV. The increase in EDV is accompanied by an increased LVEDP. Isovolumetric contraction is shortened with the ventricle reaching a peak pressure above aortic pressure through activation of the Frank-Starling mechanism to increase the force of contraction.[4]

Frank-Starling relationships

The Frank-Starling mechanism is an intrinsic cardiac response to changes in heart rate or SV (Figure 8).[8,9]

The mechanism was defined by Otto Frank in the 19th century using isolated frog hearts. He found that the strength of the ventricular contraction was increased by the level of the stretch of the ventricle before contraction. Ernest Starling and his group added to this knowledge by discovering that increased venous return increased the LVEDP, increasing the SV. On the contrary, they described the decrease in SV as related to reductions in venous return.[9,10]

Systolic dysfunction (Figure 9)

Ventricular systolic dysfunction is characterised by reduced contractility. In prolonged failure of contractility, the ventricle dilates and retains more fluid as ventricular emptying is incomplete. There is a compensatory increase in preload as SV decreases. There is a downward shift in the Frank-Starling

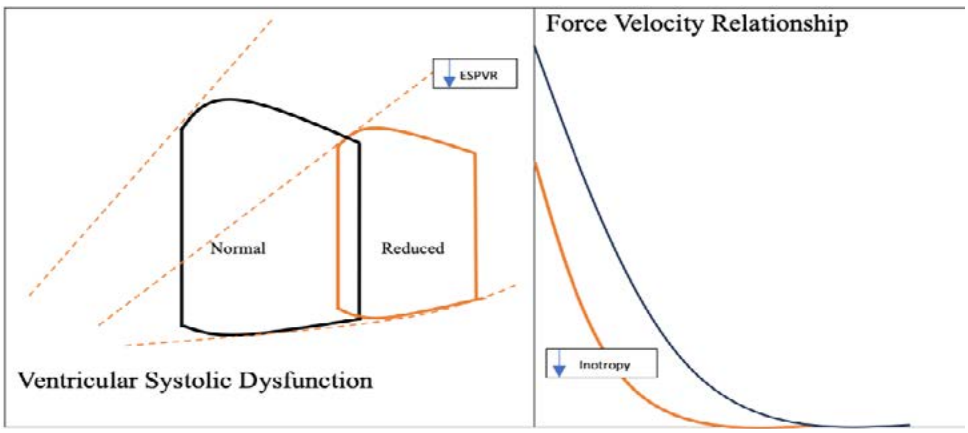


Figure 9: Ventricular systolic dysfunction

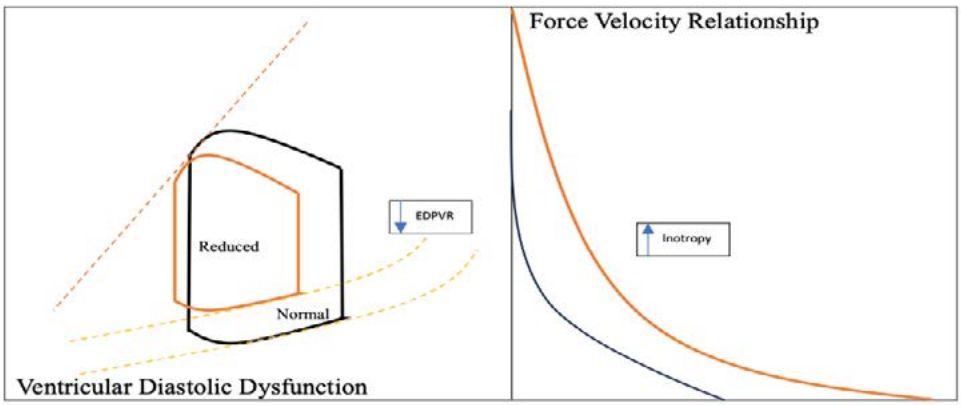


Figure 10: Ventricular diastolic dysfunction

relationship/curve.[3,4] The PV loop of a systolic dysfunctional ventricle shows an increase in ESV, a compensatory increase in EDV, reduced SV, a normal EDPVR, and a depressed ESPVR slope.[6]

Diastolic dysfunction (Figure 10)

Diastolic dysfunction occurs in ventricles that are either thickened or stiff. These ventricles have a lusitropic challenge.[3,4] The ventricle has an elevated EDV and EDP, fails to generate a supra-aortic peak pressure, and therefore eject a reduced stroke volume. The ESPVR is preserved whereas the EDPVR is reduce. Contractility may be increased.[6,11,12]

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References

1. Knottenbelt M. Pressure-volume catheter placement in the left ventricle - carotid vs. apical approach. [Internet]. ADInstruments; 2020. Available from: https://www.adinstruments.com/ blog/Left-ventricular-catheterization-carotid-vs-apical-approach. Accessed 12 October 2023.
2. Miranda-Silva D, Sequeira V, Lourenço AP, Falcão-Pires I. Assessing rodent cardiac function in vivo using hemodynamic pressure-volume loops. Front Physiol. 2022;12:751326. https://doi.org/10.3389/fphys.2021.751326.
3. Klabunde RE. Ventricular pressure-volume relationship.[Internet]. Cardiovascular physiology concepts; c1998-2023. Available from: https://cvphysiology.com/cardiacfunction/ cf024. Accessed 12 October 2023.
4. Klabunde R. Cardiovascular physiology concepts. 3rd Edition. Philadelphia: Wolters Kluwer; 2021.
5. Kaplan JA. Kaplan's Cardiac Anesthesia. 8th Edition. Philadelphia: Elsevier; 2023.
6. Klabunde R. Ventricular diastolic dysfunction. [Internet]. Cardiovascular physiology Concepts; c1998-2023. Available from: https://cvphysiology.com/heart-failure/hf006. Accessed 12 October 2023.
7. Dekker AL, Barenbrug PJ, van der Veen FH, et al. Pressure-volume loops in patients with aortic stenosis. J Heart Valve Dis. 2003;12(3):325-32.
8. Bloria SD. Lessons from the frank-starling curve. Ann Card Anaesth. 2021;24(1):118-9. https://doi.org/10.4103/aca.ACA_29_20.
9. Medert R, Bacmeister L, Segin S, Freichel M, Camacho Londoño JE. Cardiac response to β-adrenergic stimulation determined by pressure-volume loop analysis. J Vis Exp. 2021;(171). https://doi.org/10.3791/62057.
10. Han JC, Taberner AJ, Loiselle DS, Tran K. Cardiac efficiency and Starling's law of the heart. J Physiol. 2022;600(19):4265-85. https://doi.org/10.1113/JP283632.
11. Leite-Moreira AF. Current perspectives in diastolic dysfunction and diastolic heart failure. Heart. 2006;92(5):712-8. https://doi.org/10.1136/hrt.2005.062950.
12. Leite S, Rodrigues S, Tavares-Silva M, et al. Afterload-induced diastolic dysfunction contributes to high filling pressures in experimental heart failure with preserved ejection fraction. Am J Physiol Heart Circ Physiol. 2015;309(10):H1648-54. https://doi.org/10.1152/ajpheart.00397.2015.

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Cardiopulmonary interactions

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The goal of the heart and lungs is to deliver oxygen at a tissue level, and this is determined by cardiac output (CO) and the oxygen content of arterial blood (CaO_2), $DO_2 = CO \times CaO_2$.[1] The heart and lungs share the same intrathoracic space: mechanically this is akin to having a pump within a pump.[2] Cardiopulmonary interactions refer to the relationship between airway pressures, lung volumes, and CO.[3] In health, the effect of cardiopulmonary interactions is minimal. It is important to look at each part of the heart separately as phasic changes in intrathoracic pressures (ITP) have differing effects.

In a spontaneously breathing person, a negative ITP is transmitted to the right atrium. The flow of blood to the right atrium is governed by Ohm's law, flow = $\triangle P/R$, where $\triangle P$ is the driving pressure to the right atrium and R is the resistance of the capacitance vessels.[4] With positive pressure ventilation (PPV) the increased ITP is transmitted to the right atrium, which results in a reduction of the driving pressure and ultimately the venous return (VR). The right ventricle afterload is the pressure that the heart must work against to eject blood during systole, and this is determined by the pulmonary vascular resistance (PVR).

PVR is determined by the extra-alveolar vessels and the intra-alveolar vessels. The total PVR is the addition of the two and lowest at functional residual capacity.[5] The left ventricle preload is essentially equal to the right ventricle output. There is a time lag as blood must traverse the pulmonary circulation. Left ventricle afterload can be expressed as left ventricular (LV) wall stress. Afterload increases as transmural pressure and vascular resistance increase. Positive pressure reduces the transmural pressure needed for the ejection of the stroke volume. With negative ITP there is a pressure pulling outwards as the ventricle attempts to eject its stroke volume, therefore higher transmural pressures are needed.[4] Knowing how the heart and lungs work in the normal physiological state will help guide decision-making about heart-lung interactions in critically ill patients therefore mitigating any adverse consequences.

Keywords: cardiopulmonary interactions, intrathoracic pressure, spontaneous ventilation, positive pressure ventilation, pulmonary vascular resistance

Introduction

The heart and lungs work together to meet the body's tissue oxygen demands. The effect of pulmonary physiology on cardiac function is not always appreciated and this article aims to examine how the lungs may affect the cardiovascular function in healthy individuals. It is important to note that in diseased states these effects can be exaggerated, and may ultimately lead to an imbalance between tissue oxygen demand and supply resulting in tissue hypoxia and cell death.[6]

The mechanical interplay between the respiratory and cardiac systems was first observed some 300 years ago by English physiologist Stephen Hales. He noted that the level of a blood column in a glass tube inserted into a horse's carotid artery varied cyclically with respiration.[2] Hales also first documented that the blood pressure of healthy individuals fell during spontaneous respiration.[6] Cardiopulmonary interactions refer to the relationship between airway pressures, lung volumes, and CO.[3]

The heart and lungs share the same intrathoracic space, essentially it resembles having a pump within a pump. Hence the ITP and volume changes in the lungs during respiration affect the performance of the heart.[2] There are also neural and humoral mediated phenomena that act on the heart and lungs, this together with direct mechanical effects constitute heart-lung interactions.[2] To understand how breathing affects CO, it is necessary to understand the normal factors that regulate CO.[7] This is governed by the equation:[4]

CO = stroke volume × heart rate

The determinants of stroke volume are preload, afterload, and contractility. This article will examine how the lungs affects the heart. It is important to consider each ventricle separately, as changes in intrathoracic pressure during spontaneous ventilation and PPV have differing effects on the ventricles.[1]

Right ventricular (RV) preload

The preload is essentially the end-diastolic volume (EDV). It depends on the VR, which in turn depends on the driving pressure between the extrathoracic great veins (EGV) and the

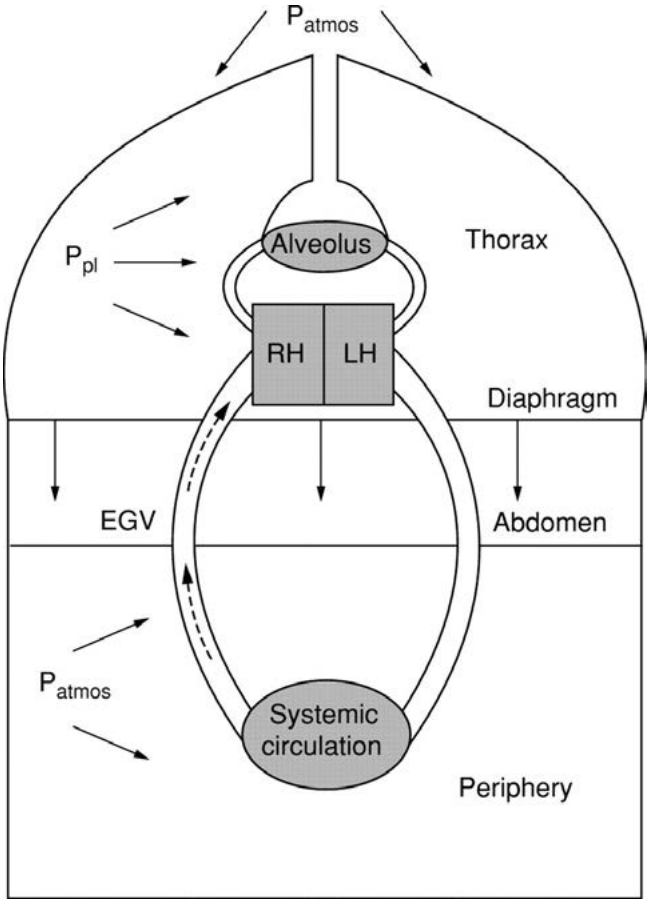

Figure 1: Model of the circulation showing factors that influence systemic venous drainage.[6]

$$\text{Flow} = \frac{\text{Driving pressure}}{\text{Resistance}} \text{ therefore, VR (dotted line)} = \frac{\text{EGV-Right arterial pressure}}{\text{Resistance}}$$

pressure in the right atrium. There is also the resistance to VR to consider, as determined by Ohm's law: Flow = $\frac{\triangle P}{R}$. The gradient for VR is equal to the difference between the mean systemic venous pressure (Msvp), or EGV, and the right atrial pressure (Rap) as seen in figure 1.[2] The right heart (RH), and intrathoracic great veins are subjected to pleural pressure (P_{pl}). Therefore, during spontaneous ventilation, also known as negative pressure ventilation, the ITP decreases, and this is transmitted to the right atrium. This increases the driving pressure and thus makes it easier for blood to return.

Additionally, as you breathe in your diaphragm moves down, and the intra-abdominal pressure increases, resulting in an increased pressure in the EGV, this normalises to atmospheric (P_{atmos}) with expiration. The combined benefit of increased upstream pressure and decreased downstream pressure works to increase VR in the right atrium.[4] The opposite occurs when PPV is introduced. The increased ITP is transmitted to the right atrium, this reduces the gradient for the driving pressure, and thus the preload. At the initiation of PPV, there is a drop in CO because there is not as much VR.

LV preload

LV preload is equal to RV output. Therefore, a decreased RV stroke volume, regardless of the cause, translates to reduced LV preload. There is a slight lag in time as the blood must traverse the pulmonary circulation. LV preload cannot be discussed without mentioning RV afterload as this influences the blood going to the left atrium. It is governed by the equation:[4]

$$\text{Pulmonary venous return} = \frac{\text{Pmv-Pla}}{\text{Rpv}}$$

Where: Pmv = mean pulmonary pressure, Pla = left atrial pressure, Rpv = pulmonary venous resistance

RV afterload

RV afterload is the load the RV cardiac myocytes have to overcome to contract, as determined by the PVR.[3] In other words, the RV afterload is known as the RV systolic wall tension. RV wall tension is approximately described by Laplace's equation for a spherical chamber:[8]

$$\text{Wall tension} = \frac{\text{Ptm x r}}{\text{2 x h}}$$

Where: Ptm= RV transmural pressure, r = radius, h = wall thickness

The systolic RV pressure is the transmural pressure. Transmural pressure is the pulmonary artery pressure minus the ITP.[8] The right ventricle output flows through the pulmonary vasculature, generally a low-pressure system that will ultimately determine the left ventricle preload. RV output is dependent upon RV preload, contractility, and afterload, and afterload is proportional to PVR. PVR is influenced by changes in the lungs' volumes during inflation and deflation. The alveolar oxygen tension, pH, and partial pressure of carbon dioxide (pCO_2) may also alter the PVR to an extent.[8]

The PVR is a function of the extra-alveolar and intra-alveolar vessels. The pulmonary vasculature can be divided into extra-alveolar vessels and intra-alveolar vessels. The extra alveolar vessels are large capacitance vessels and run along the lung interstitium, they are kept open by increased lung volumes as radial traction pulls them open. Therefore, at high lung volumes, they cause a decrease in the PVR.[2,8] At low lung volumes the interstitial traction decreases, reducing the cross-sectional diameter, thereby causing an increase in PVR.

In the intra-alveolar vessels, the reverse happens. At high lung volumes, the intra-alveolar vessels which are surrounded by alveoli are squashed and their cross-sectional diameter decreases, leading to an increase in PVR. At low lung volumes the intra-alveolar diameter is at its largest and PVR is minimal. These PVR changes are illustrated in Figure 2.[9] The net PVR is a result of the additive effect of the two forces. At functional residual capacity (FRC) the overall PVR is minimal. Therefore, the goal is to ventilate to FRC. Alveolar hypoxia, hypoventilation, and resorption atelectasis may occur at volumes below FRC. This may lead to hypoxic pulmonary vasoconstriction (HPV), which further increases PVR.[1] Alveolar hypoxia can increase PVR, and hypocapnia can reduce PVR.[3]

It is worth mentioning that when positive end-expiratory pressure (PEEP) is applied to the alveolar for recruitment purposes and the alveoli are open to receive oxygen, HPV will be diminished,

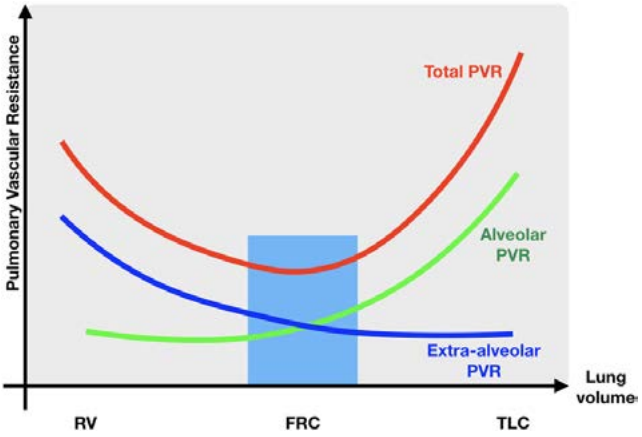

Figure 2: Relationship between PVR and lung volume
RV = residual volume, TLC = total lung capacity[9]

thus decreasing their contribution to an increased PVR. The recruitment of previously closed capillaries occurs when the lungs are opened by exposure to higher upstream pressures, this recruitment increases the total volume available for RV CO and reduces resistance to flow.[9] The caveat is significantly increased tidal volumes, such that the lung is overdistended, results in an increase in PVR and ultimately leads to a decrease in CO. This effect is exacerbated with excessive use of PEEP.[1]

Distribution of pulmonary blood flow

Gravity and HPV are the major determinants of pulmonary blood flow. Perfusion to an alveolus is dependent on the relationship between the pulmonary alveolus pressure (P_A), the pulmonary arteriolar pressure (P_a), and the pulmonary venous pressure (P_v).[1]

- In west zone I, $P_A > P_a > P_V$ resulting in compression of the vessels and dead space ventilation. This does not normally occur in healthy individuals.
- In west zone II, $P_a > P_A > P_V$, there is pulmonary blood flow mainly in systole.
- In west zone III, $P_a > P_V > P_A$, there is blood flow in systole and diastole.

During mechanical ventilation, positive pressure can create more zone I and zone II areas and alter zone III areas. This creates more resistance and RV afterload dead space ventilation and potential increased shunt flow.[10]

LV afterload

This is the pressure the heart must overcome to be able to eject blood during systole. It is also referred to as ventricular wall stress. The pressure is significantly greater than the pressure generated by the right ventricle. This wall stress is governed by the law of Laplace as seen in Figure 3.[2,4] It is proportional to the pressure within the cavity and the radius, and inversely proportional to the width of the chamber.

$$T\alpha = \frac{P \times r}{u}$$

Transmural pressure is the "actual working" pressure that the wall heart chambers have to generate (Figure 4).[2] The immediate pressure around the heart is the pericardial pressure; however, in

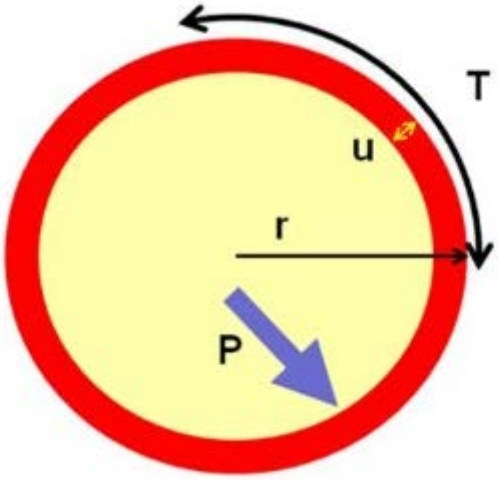

Figure 3: Demonstration of factors influencing LV afterload[11]
T – wall stress, P – transmural pressure, r – radius, u – wall thickness

the absence of pericardial disease, pericardial pressure is equal to the pleural pressure. Pleural pressure varies cyclically with inspiration and expiration.

Transmural pressure = intracavitary pressure - surrounding pressure

During spontaneous negative breathing, the thorax exerts an outward negative pressure, this creates extra pressure on the ventricle that is trying to contract. The opposite occurs with PPV; the surrounding pressure on the heart pushes inwards and thus decreases the wall stress on the LV and allows the LV to contract better. In a way, the positive ventilation acts as an LV assist device. As seen below in Figure 5a, if the ITP is -20 mmHg, to generate 80 mmHg in the aorta, the ventricle must contract strongly to overcome the -20 mmHg. It will have to generate 100 mmHg effectively and thus work harder. If the pleural pressure is +20 mmHg (Figure 5b), the ventricle will have to generate 60 mmHg to measure a pressure of 80 mmHg in the aorta.

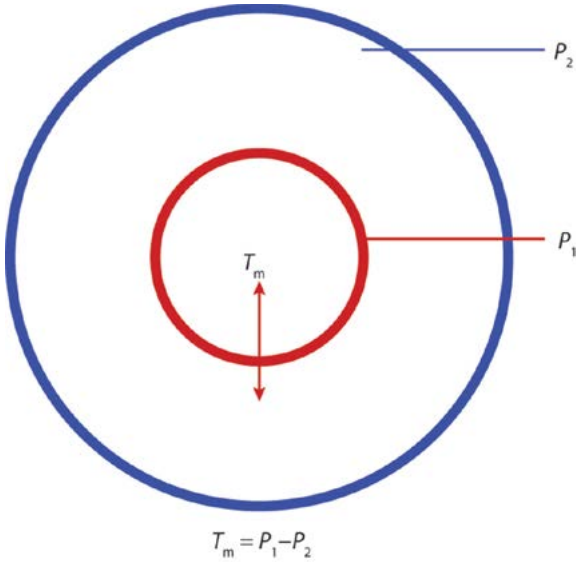

Figure 4: Transmural pressure is the net pressure experienced by the inner chamber walls.
T_m = transmural pressure, P_1 = pressure in the inner chamber, P_2 = pressure in the outer chamber

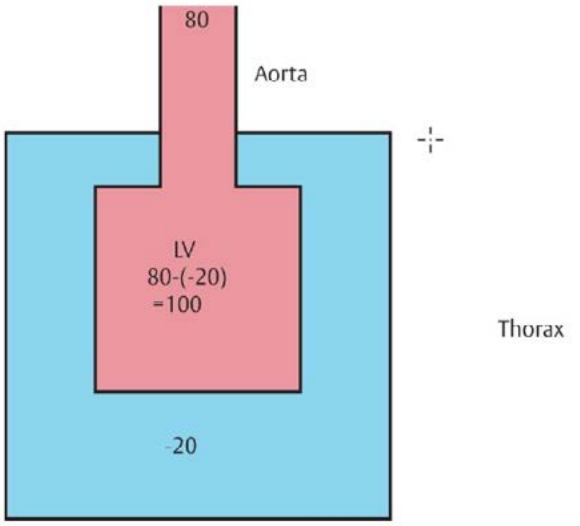

Figure 5a (left): Spontaneous negative pressure;

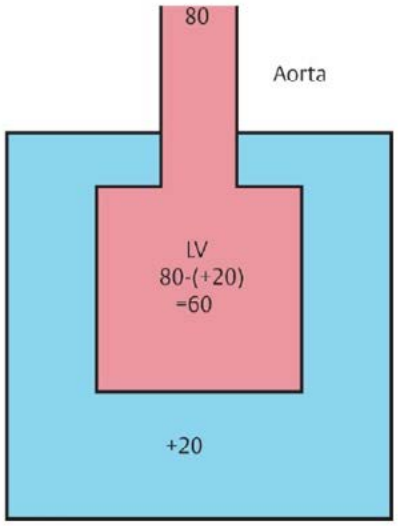

Figure 5b (right): PPV.

The afterload is determined by transmural pressure and systemic vascular resistance (SVR). The SVR is largely unaltered by respiration; it is the transmural pressure during breathing that influences the afterload. In diseased states, such as acute bronchospasm, LV afterload is exacerbated by excessive negative ITP, which may potentially precipitate acute LV dysfunction.[4]

Ventricular interdependence

The right and left ventricles share a pericardial space. Therefore, volumes and pressures on one side will ultimately affect volumes and pressures on the other side, this phenomenon is known as ventricular interdependence.[2] During normal spontaneous respiration, there is an increase in VR and RV filling and pressure, causing a slight shift of the interventricular septum to the left, as seen in Figure 6.[5] This leads to less space for the LV to fill, thus the LV output decreases and leads to a normal fall in systolic blood pressure on inspiration. On expiration, the opposite happens where there is an increase in ITP, less RV preload, and RV filling, the LV can fill better, and the systolic blood pressure goes back to normal.

In normal, healthy individuals with normal spontaneous ventilation, this is not an issue. However, in a case of acute obstruction, where one takes large negative breaths, the RV preload increases significantly and the right-sided EDV increases, ultimately affecting the filling of the LV, due to the bowing of the interventricular septum.[4] This phenomenon of drop in blood pressure is known as pulsus paradoxus.[4] During excessive ventilation, the lungs can expand significantly, and the PVR will increase and result in an increased right-sided EDV, which can impair LV filling and CO.

Lung volumes and ventricular contractility

Ventricular contractility is determined by preload-dependent and preload-independent variables. Preload-dependent variables include the Frank-Starling mechanism whereby an increase in preload results in an increase in stroke volume up to a point. PEEP affects these preload-dependent variables.[3] Preload-independent mechanisms will not be affected by PEEP but by the tidal volumes and ITP by their activation of lung stretch receptors, which affects chronotropic, inotropy, and systemic vasodilation. Consequently, a response known as "lung-inflation vasodepressor reflex" is activated, resulting in dilation of systemic vessels and negative inotropy.[3]

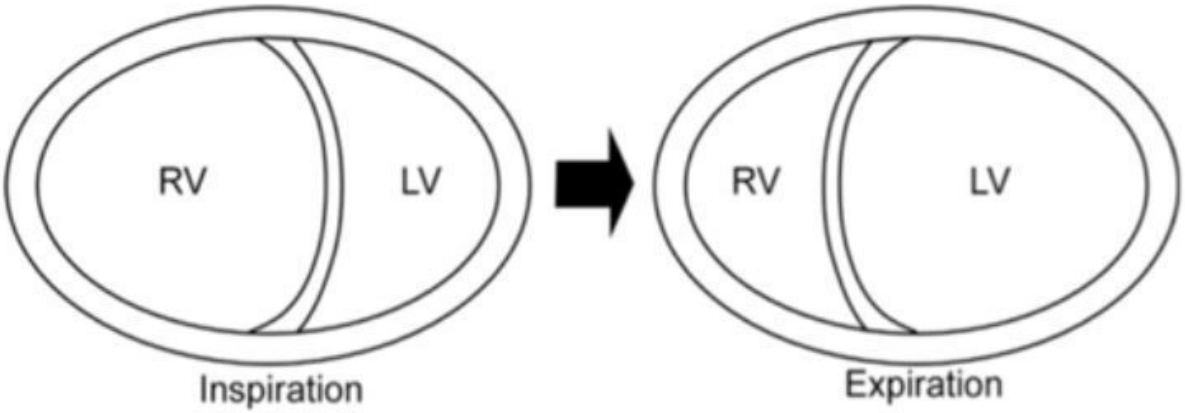

Figure 6: Cyclical respiratory variation of LV filling

Consolidated effect of spontaneous ventilation

- As ITP ↓ there is ↑ VR to the RH.
- RV afterload ↓ due to fall in PVR (secondary to lung inflation to FRC).
- The combined effect leads to ↑ RV output; however, takes time to traverse pulmonary circulation.
- Simultaneously LV preload decreases due to immediate pooling of blood in pulmonary circulation on inspiration.
- LV afterload and transmural pressure ↑ due to negative ITP.
- Leads to ↓ LV stroke volume seen as ↓ systolic and pulse pressure on arterial pressure waveform.
- At expiration, the increased portion of RV output generated from inspiration reaches the LV, this manifests as ↑ LV stroke volume and ↑ systolic and pulse pressure on the arterial trace.

Consolidated effect of mechanical ventilation

- With PPV the ITP ↑ results in a ↓ VR.
- RV afterload ↑ due to a rise in PVR (occurs with lung overinflation).
- Thus, RV output ↓; however, takes time to traverse the pulmonary circulation before it becomes LV preload.
- Simultaneously LV preload ↑ due to squeezing of blood out of the pulmonary circulation by ↑ ITP.
- LV afterload and transmural pressure ↓ leading to ↑ systolic and ↑ pulse pressure on the arterial trace.
- At expiration, the ↓ RV output produced during inspiration reaches the LV and manifests as ↓ LV stroke volume and ↓ systolic and pulse pressure on the arterial pressure trace.

Clinical implications of cardiopulmonary interactions

In a patient with LV failure, which may manifest as pulmonary rales, low blood pressure, and low arterial oxygen content, PPV assists the LV by lowering the LV afterload. PPV may also help to recruit closed alveoli and thus mitigate the effects of hypoxic pulmonary vasoconstriction. PPV on the PVR is the sum of vasodilation caused by alveolar reoxygenation and vasoconstriction mediated by pulmonary vasculature stretch at volumes greater than FRC. PPV reduces the respiratory work of patients, which reduces their metabolic demands, and in turn, reduces the required cardiopulmonary interactions.

In patients with obstructive lung disease who are breathing spontaneously, they must generate large negative ITP during respiration. In the patient with a compromised LV function, this may be detrimental as their LV has a much larger LV afterload to overcome.

Pulse pressure variation can be used as a surrogate for stroke volume variation (SVV). A pulse pressure variation > 12% is strongly associated with fluid responsiveness. SVV is based on the same principle as pulse pressure variation, thus SVV > 10% is associated with fluid responsiveness.

Conclusion

The heart and lungs are inextricably linked as they share a common space. Lung volumes and ITP affect CO and the determinants of stroke volume. A good understanding of how the pressures in the thorax affect the CO in a healthy individual is important as these effects are exaggerated in disease. This will have an important bearing on how one can ventilate and manage critically ill patients in the intensive care unit setting and mitigate the adverse effects of cardiopulmonary interactions.

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References

1. Williams E, Whitney G. Cardiopulmonary interactions. Southern African Journal of Critical Care. 2006;22(1).
2. Kochhar G, Mehta Y, Trehan N. Heart-lung interaction. J Card Crit Care. 2018;2(2):61-5. https://doi.org/10.1055/s-0039-1685130.
3. Stigall WL, Willis BC. Mechanical ventilation, cardiopulmonary interactions, and pulmonary issues in Children with Critical Cardiac Disease. In: Da Cruz EM, Ivy D, Jaggers J, editors. Pediatric and Congenital Cardiology, Cardiac Surgery and Intensive Care [Internet]. London: Springer London; 2014. p. 3147-81. https://doi.org/10.1007/978-1-4471-4619-3_175.
4. Rettig J. Cardiopulmonary interactions [Internet]. 2019 [cited 2023 Aug 22]. Available from: https://youtu.be/9KQ8O0b6RKs?si+hgryZ_igwF2pNJM.
5. Bronicki RA, Penny DJ, Anas NG, Fuhrman B. Cardiopulmonary interactions. Pediatric Critical Care Medicine. 2016;17:S182-93. https://doi.org/10.1097/PCC.0000000000000829.
6. Shekerdemian L, Bohn D. Cardiovascular effects of mechanical ventilation. Archives of Disease in Childhood. 1999;80(5):475-80. https://doi.org/10.1136/adc.80.5.475.
7. Magder S. Heart-Lung interaction in spontaneous breathing subjects: the basics. Ann Transl Med. 2018];6(18):348-348. https://doi.org/10.21037/atm.2018.06.19.
8. Steingrub JS, Tidswell M, Higgins TL. Hemodynamic consequences of heart-lung interactions. J Intensive Care Med. 2003;18(2):92-9. https://doi.org/10.1177/0885066602250369.
9. Vrancken SL, Van Heijst AF, De Boode WP. Neonatal hemodynamics: From developmental physiology to comprehensive monitoring. Front Pediatr. 2018;6:87. https://doi.org/10.3389/fped.2018.00087.
10. Mahmood SS, Pinsky MR. Heart-lung interactions during mechanical ventilation: the basics. Ann Transl Med. 2018;6(18):349-349. https://doi.org/10.21037/atm.2018.04.29.
11. Met N. Ventricular wall tension and La Place relationship [Internet]. 2019 [cited 2023 Aug 29]. Available from: https;//greek.doctor/second-year/physiology-1/31-ventricular-wall-tension-and-the-laplace-relationship/.

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FCA REFRESHER COURSE

Physiology of excitable tissue

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The four basic types of tissue found in the body are connective tissue, epithelial tissue, muscle tissue, and nervous tissue. Nerves and muscles are capable of generating and propagating action potentials (APs). They are therefore called excitable tissues. Excitation of these tissues may be electrical, chemical, or mechanical. The human body relies on the proper functioning of excitable tissues to facilitate vital physiological processes, including muscle contraction, nerve conduction, and cardiac activity.[1,2]

Nerve tissue comprises neurons, which are responsible for transmitting electrical signals, while muscle tissue generates mechanical force in response to electrical stimulation. These tissues share common characteristics related to their excitability, AP generation, and conduction properties.[1,2] The ability of excitable tissue to generate and propagate APs depends upon the electrical properties of the cell membrane at rest.[3]

The resting membrane potential (RMP)

An electrical potential difference exists across all cell membranes. The RMP of a cell is defined as the electrical potential difference across the cell membrane when that cell is in a non-excited state.[1,2]

The cytosol along the inner surface of the membrane has a negative charge compared to the outside. Excitable tissues have a more negative RMP when compared to non-excitable tissues. The negative RMP is an absolute requirement for a functioning nervous system and is generated by the distribution of certain important ions across the cell membrane. The RMP in the neuron is -70 millivolts (mV) and -90 mV in skeletal and cardiac muscle fibres.[1–3]

The RMP of a cell depends on the ionic distribution across the membrane, the membrane permeability, and other factors like the presence of ion channels and the sodium-potassium (Na^+/K^+) pump.[1]

Movement of ions

Most electrically charged ions on either side of a phospholipid bilayer membrane can only pass across the membrane through protein/ion channels as the membrane is only semipermeable to ions. Although ion channels allow the movement of ions across the cell membrane, the mere opening of these channels does not result in the movement of ions across the membrane. Instead, an external force, more often a chemical or electrical gradient, is required to drive this movement.[1–3]

The chemical movement of ions (diffusion): Diffusion entails ions shifting from high to low concentration areas, usually through the ion-permeable channels.[1,3]

The electrical movement of ions: Ions, being electrically charged, move continuously across the phospholipid bilayer in response to an applied electrical field, until an electrochemical equilibrium is reached.[1,3]

At equilibrium, the chemical driving force is balanced by the electrical driving force of an ion.[1] The Gibbs-Donnan theory describes the unequal distribution of permeant charged ions on either side of a semipermeable membrane, which occurs in the presence of impermeant charged ions. In this state, the electrical and chemical energies on both sides of the membrane are balanced despite the difference in ion concentrations on either side of the membrane.[1]

If the relative concentration of an ion across a cell membrane is known, the Nernst equation can be used to calculate the equilibrium potential (Nernst potential) of that ion along this membrane (Figure 1a). The Nernst potential denotes the precise potential difference across the membrane that prevents the overall movement of an ion in either direction through the membrane. This concept is valuable for understanding how ions contribute to the electrical behaviour of excitable cells.[1–4] When using this equation, the calculated Nernst potential is the potential inside the membrane, and the sign of the potential is positive if the ion under consideration is a negative ion, and negative if it is a positive ion.[1,3]

Understanding the Nernst equation and equilibrium potentials explains how changes in ion concentrations or shifts in ion channel permeability impact the electrical excitability and functioning of excitable tissues. Given that, at a state of rest and

a) The **Nernst equation** for any univalent ion at a normal body temperature of 37°C:

$$\text{EMF(millivolts)} = \pm 61 \log \frac{C1}{C2}$$

Where:
EMF is the electromotive force (voltage) for the ion of interest.
C1 is concentration of the ion inside.
C2 is the concentration of the ion outside.

b) The **Goldman constant field equation** (Goldman- Hodgkin-Katz equation):

$$\text{EMF (millivolts)} = -61 \times \log \frac{C_{Na_i^+} P_{Na^+} + C_{K_i^+} P_{K^+} + C_{Cl_o^-} P_{Cl^-}}{C_{Na_o^+} P_{Na^+} + C_{K_o^+} P_{K^+} + C_{Cl_i^-} P_{Cl^-}}$$

Where:
P is permeability to each ion
C is concentration of each ion

Figure 1: Nernst and Goldman constant field equations

normal body temperature, the cell membrane is predominantly permeable to potassium ions, it is understandable that the calculated Nernst potential of -80 mV for potassium aligns closely with the RMP observed in many excitable cells.[1,3]

As the membrane is permeable to several different ions, the actual RMP that develops depends on the polarity of each ion, the membrane permeability of each ion, and the ionic concentration on either side of the membrane. This can be calculated using the Goldman constant field equation (Figure 1b).[1,3]

Ion channels and pumps

An ion channel is a protein-based "channel" consisting of four to six protein molecules that traverse the cell membrane, allowing the transit of one or more ions. The configuration of these subunits varies across different channels.[1–4]

The sodium-potassium pump (Na^+/K^+ pump)

All cell membranes contain a potent electrogenic pump reliant on energy – the Na^+/K^+ pump. This pump operates continuously, pumping $3Na^+$ ions out of the cell while pumping in $2K^+$ ions. Consequently, a surplus of positive ions outside the cell leads to a negative intracellular charge. Additionally, this pump gives rise to substantial concentration differences of Na^+ and K^+ across the resting membrane.[1,2]

The potassium-sodium "leak" channel (K^+/Na^+ "leak" channels)

These channels are around 100 times more permeable to K^+ compared to Na^+, resulting in a much greater leakage of K^+ ions than Na^+ ions during rest. Thus, the diffusion of K^+ makes a significantly more substantial contribution to the RMP when compared to the diffusion of Na^+.[1,2]

Voltage-gated sodium channels (Na^+ channels)

The voltage-gated Na^+ channel has two gates: the activation gate, positioned near the outside of the channel; and the inactivation gate, situated closer to the inside of the channel. When the cell is at rest, the activation gate remains closed, preventing the influx of Na^+ ions. As the membrane potential becomes less negative (between -70 and -50 mV), the activation gate undergoes a conformational change, allowing it to open. This change in voltage also results in a conformational change of the inactivation gate leading to its closure, albeit at a slower pace. This means the inactivation gate takes a fraction of a second longer to close compared to the time it takes for the activation gate to open, allowing Na^+ to leak in. The inactivation gate remains closed until the membrane potential reverts to or closely approaches the original RMP.[1,2]

The operational behaviour of Na^+ channels is influenced by the concentration of extracellular calcium (Ca^{2+}). A reduction in extracellular Ca^{2+} levels enhances the ease of activation of Na^+ channels, causing them to open with a lesser alteration in the membrane potential. As a result, nerve fibres become notably more excitable in patients with hypocalcaemia.[2]

Voltage-gated potassium channels (K^+ channels)

The voltage-gated K^+ channel has one gate that remains closed during the resting state. When the membrane potential becomes less negative, this gate undergoes a slow conformational change, occurring as the Na^+ channels close, resulting in the gate opening and allowing K^+ ions to diffuse outwards.[1,2]

The calcium pump (Ca^{2+} pump)

Almost all cell membranes have a Ca^{2+} pump, like the Na^+ pump, that pumps Ca^{2+} out of the cell.[1,2]

Voltage-gated calcium channels (Ca^{2+} channels)

These are found predominantly in cardiac and smooth muscle. They are partially permeable to Na^+ and permeable to Ca^{2+}. They are called slow channels as they take 10 to 20 times longer than the Na^+ channels to open. When they open, both Na^+ and Ca^{2+} flow inside.[1,2]

The AP

Signals are transmitted by APs, which are simply rapid, brief reversals of the RMP so the inside of the cell becomes positive compared to the outside and then ends with an almost equally rapid change back to the negative potential.[3] APs occur to produce physiological effects, such as the transmission of

impulses along nerve fibres, the release of neurotransmitters, muscle contractions, and activation or inhibition of glandular secretions.[1–4]

Stages of the AP (Figure 2)

Resting stage: The membrane is "polarised" during this stage with a negative membrane potential. The voltage-gated Na^+ channel has its activation gate closed and its inactivation gate opened. The voltage-gated K^+ channel is closed.[1–4]

Depolarisation stage: During this stage, any event causing the membrane potential to become less negative results in a conformational change in the activation gate of the voltage-gated Na^+ channel, causing it to open, increasing the membrane's Na^+ permeability by as much as 500–5 000-fold. With the movement of Na^+ ions inside, the membrane potential rises rapidly in the positive direction. In large nerve fibres, the membrane potential overshoots beyond the zero level and becomes slightly positive. In smaller fibres, the membrane potential merely approaches the zero level and does not overshoot to the positive state.[1–4]

Plateau (only in some APs) (Figure 3): This occurs when the excitable membrane does not repolarise immediately after depolarisation but instead the potential remains on a plateau near the peak of the spike for a few milliseconds before repolarisation. This occurs in heart muscle because of two factors: firstly, the presence of slow voltage-activated Ca^{2+} channels; and secondly, the K^+ channels are slower to open, thus delaying the return of the membrane potential to the resting state. The slow Ca^{2+} channels start opening later than the Na^+ channels and allow the movement of Ca^{2+} and a little Na^+ into the cell. They also remain open for longer, thus resulting in the plateau of the AP.[1,2]

Repolarisation stage: In most APs during this stage (a fraction of a second after the activation gate of the Na^+ channel opens) the inactivation gate of the Na^+ channels begins to close and the voltage-gated K^+ channels open. This allows rapid diffusion of K^+ to the outside, which re-establishes the normal negative RMP (repolarisation of the membrane).[1–4]

"Positive" afterpotential/hyperpolarisation: After repolarisation, the membrane potential becomes more negative than the original RMP for a few milliseconds. This occurs because the voltage-gated K^+ channels remain open for a few milliseconds after repolarisation, allowing K^+ to flow out and make the inside more negative.[1,3]

Propagation of the AP: An AP elicited at a point on an excitable membrane will usually excite the adjacent portions, which will result in the propagation of the AP. This propagation will occur in both directions away from the stimulus until the entire membrane has been depolarised. The depolarisation process that travels along the length of the nerve or muscle fibre is called a nerve or muscle impulse. In the neuron, a nerve impulse carries information along the neuron to the central nervous system (sensory fibre) or they conduct signals from the central nervous system to the periphery (motor fibre). In the muscle cell, the

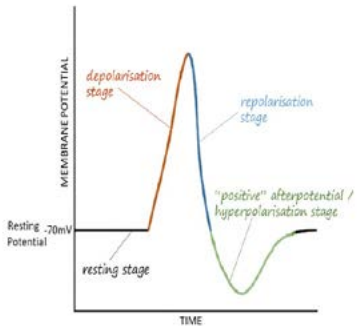

Figure 2: Stages of an AP

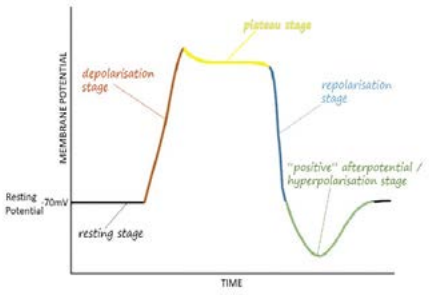

Figure 3: AP with plateau phase

muscle impulse spreads all over the muscle to initiate muscle contraction required for all motor activities. The duration of APs in skeletal muscle and neurons is about five milliseconds.[1,2]

Recharging: Finally, the Na^+ and K^+ ion concentration differences across the membrane need to be re-established. This is achieved by the energy-requiring Na^+/ K^+ pump, pumping Na^+ out of and K^+ into the cell. The activity of the Na^+/ K^+ ATPase pump increases approximately in proportion to the third power of the increase of the Na^+ concentration inside the cell.[4]

Important terminology (Figure 4)

The threshold for initiation of an AP: The membrane potential at which the occurrence of the AP is inevitable. This occurs when enough voltage-gated Na^+ channels are opened, resulting in the relative ionic permeability of the membrane favouring Na^+ over K^+.[1–3]

Acute subthreshold potential: If a stimulus does not result in the threshold current being reached, then an AP will not be generated.[1–3]

Accommodation of the membrane: If the stimulating current rises too slowly, then an AP will not be generated because the neuron will adapt. This occurs because the inactivation Na^+ gates start to close during depolarisation and remain closed.[3]

All-or-nothing principle: Once the threshold value for excitation is reached, a full AP is produced. Any further increases in stimulation intensity will not result in any change in the AP.[1–3]

Absolute refractory period: The period during which a second AP cannot be elicited, even with a strong stimulus. Voltage-

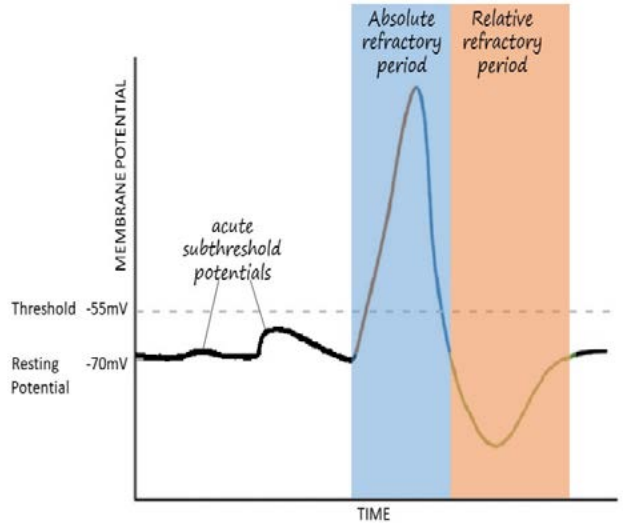

Figure 4: Acute subthreshold potentials, absolute and relative refractory periods

gated Na^+ channels are inactivated by a strongly depolarised membrane. Therefore, they cannot be activated until the membrane potential has become sufficiently negative.[1–3]

Relative refractory period: New APs can be triggered if the stimulus is greater than normal. In this period the membrane is hyperpolarised due to the continued activation of voltage-gated K^+ channels, but voltage-gated Na^+ channels are reactivated.[1–3]

Generation of multiple APs: Multiple APs will be produced if a stimulating current is applied to a neuron. The frequency of firing will increase in proportion to the magnitude of the stimulus current until a maximum firing frequency is reached (usually around 100 Hz).[3]

Orthodromic conduction: In humans and other mammals, conduction is normally in one direction only, from a receptor or synapse to their termination. Conduction in the other direction (antidromic conduction) will be prevented by the first synapse encountered.[3]

Saltatory conduction (Figure 5)

The speed at which an AP propagates in nerves depends on the axon diameter and whether it is myelinated or not. The larger the axon diameter, the faster the conduction of the impulse.[3]

Myelin is a fatty substance that forms a protective sheath around the axons of neurons. Schwann cells are a type of glial cell found in the peripheral nervous system (PNS). Schwann cells play a crucial role in the formation and maintenance of myelin sheaths around axons in the PNS. Oligodendrocytes form myelin around neurons in the central nervous system. Nodes of Ranvier are small gaps or interruptions in the myelin sheath along the length of an axon.[5]

Myelin is an extremely effective insulator that prevents APs from being transmitted regularly along the neuronal cell membrane. The AP "jumps" from one node of Ranvier to the next. This is called saltatory conduction. In this situation, the current sink

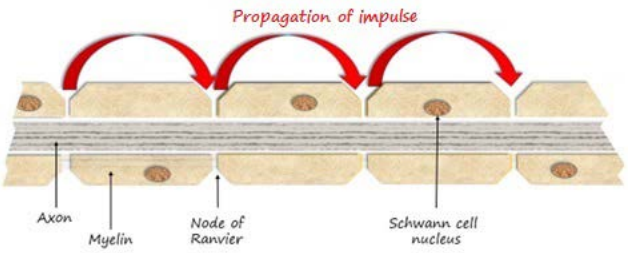

Figure 5: Saltatory conduction

at one node of Ranvier acts to depolarise the cell membrane at the next node. Saltatory conduction velocities may be up to 50 times faster than unmyelinated nerve conduction velocities and conserve energy because only the nodes depolarise.[1–5]

Synaptic transmission

A synapse, also known as a neuronal junction, is where electrical nerve impulses are transmitted between two neurons or between a neuron and a muscle cell or gland. When a neuron connects with a muscle cell, it forms a neuromuscular junction.[1,2]

Two primary categories of synapses

Electrical synapses: These occur when two cells are interconnected through gap junctions. These junctions facilitate the flow of current between cells via nonselective pores.[2]

Chemical synapses: In this type of synapse, a chemical transmitter is released by one cell and it influences the activity of another cell. Chemical synapses exhibit the following functional characteristics:

- neurotransmitter chemicals are stored in vesicles within the presynaptic terminals;
- the synaptic cleft refers to the small gap that separates two adjacent neurons; and
- the postsynaptic neuron is the recipient of the chemical signal.

When APs occur in the presynaptic cell, they trigger the release of chemical neurotransmitters. This neurotransmitter traverses the narrow synaptic cleft and binds to specific receptors on the postsynaptic cell. Excitatory neurotransmitters, like glutamate, elicit an excitatory postsynaptic potential, while inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) generate an inhibitory postsynaptic potential.[1,2]

The neuromuscular junction

Skeletal muscle fibres are voluntary muscles innervated by motor neurons. When a motor neuron reaches a muscle, its axon transforms where the myelin sheath stops and the axon branches out into multiple extensions. Each of these branches forms a distinct connection with an individual muscle fibre. This point of connection between the motor neuron and the muscle fibre is referred to as the neuromuscular junction.[2]

Upon the arrival of an AP at the axon terminal of a motor neuron, acetylcholine (ACh) is released. ACh binds to the plasma

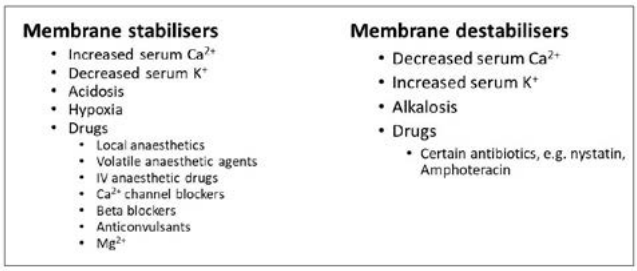

Figure 6: Membrane stabilisers and destabilisers[1,2,4]

membrane of the muscle, resulting in the opening of Na^+ channels. This event triggers an AP in the muscle membrane, which then propagates throughout the entire muscle fibre via transverse tubules (t-tubules). This propagation sets in motion the process of muscle contraction, known as excitation-contraction coupling.[1,2]

Effects of anaesthetic agents on excitable tissue

Anaesthetic agents exert their effects on excitable tissue by modulating ion channels and altering neurotransmitter function. For example, inhalational anaesthetics enhance the inhibitory function of GABA receptors, resulting in neuronal hyperpolarisation and decreased excitability. Intravenous anaesthetics, such as propofol and barbiturates, potentiate inhibitory neurotransmission through GABA receptors too. Local anaesthetics block voltage-gated Na^+ channels, preventing the generation and conduction of APs in sensory neurons.[6]

Membrane stabilisers and destabilisers (Figure 6)

Membrane stabilisers and destabilisers affect the RMP and AP of cells. Membrane stabilisers increase the threshold for depolarisation and decrease the rate of rise of the AP. Conversely, membrane destabilisers decrease the threshold for depolarisation and increase the rate of rise of the AP.[1,2,4]

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References

1. Guyton AC, Hall JE. Guyton and Hall textbook of medical physiology. 13th ed. Philadelphia: Elsevier; 2016. p. 61-73.
2. Barrett KE, Barman SM, Brooks HL, Yuan JJ, editors. Ganong's review of medical physiology. 26th ed. New York: McGraw Hill; 2019.
3. Anaesthetics JW. Anaesthesia tutorial of the week 173 8th March 2010.
4. Weerasinghe V. Excitable tissues, resting membrane potential & action potential. Faculty of Medicine, University of Peradenyia. Available from: chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://med.pdn.ac.lk/groups/lecture_notes/prof_vajira/Y1S1%20membrane%20potentials.pdf
5. Susuki K. Myelin: a special membrane for cell communication. Nat Educ. 2010;3(9):59.
6. Friederich P. Basic concepts of ion channel physiology and anaesthetic drug effects. Eur J Anaesthesiol. 2003;20(5):343-53. https://doi.org/10.1017/S026502150300053X.

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Antiarrhythmic drugs

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Cardiac muscle is unique in that it has automated or pacemaker cells and non-automated (contractile) cells. Pacemaker cells are found in the sinoatrial (SA) node, atrioventricular (AV) node, and the conduction system of the heart, while contractile cells are found in the atria and ventricles. The cardiac action potential (AP) of both these cell groups differs and results from the sequential changes in membrane permeability to Na^+, K^+, and Ca^{2+} and the flow of these ions through ion channels.

Understanding the physiology of cardiac conduction enables the understanding of the pathophysiology of arrhythmogenesis and the targets of antiarrhythmic drugs (AADs). The Singh Vaughan-Williams framework is the simplest classification system for AADs and is based on the main mechanism of action of each drug. It has recently been expanded to include previously unclassified AADs and broaden the mechanisms of action. The pharmacology and clinical applications of commonly used AADs are discussed.

Keywords: antiarrhythmic, pharmacology, cardiac action potential, pacemaker potential, arrhythmogenesis, Singh Vaughan-Williams

Cardiac action potentials (APs)

The heart is different from other tissues as it consists of automated (pacemaker) and non-automated (contractile or cardiac) cells, each with a different morphology of the AP (Figure 1).[1-3] The cardiac AP results from the sequential changes in membrane permeability to Na^+, K^+, and Ca^{2+} and the flow of these ions through ion channels.[1-3]

Non-automated or contractile cells have a stable resting membrane potential (RMP) of -90 mV.[2,3] The AP is divided into five phases based on the sequential changes in the permeability of Na^+, K^+, and Ca^{2+} flow via their respective ion channels.[1,3] There are two types of Ca^{2+} channels in the heart involved in the cardiac AP: L-type (low-threshold) and T-type (transient).[3,5] Figure 2 illustrates the phases of the AP and the action of AADs at each phase.

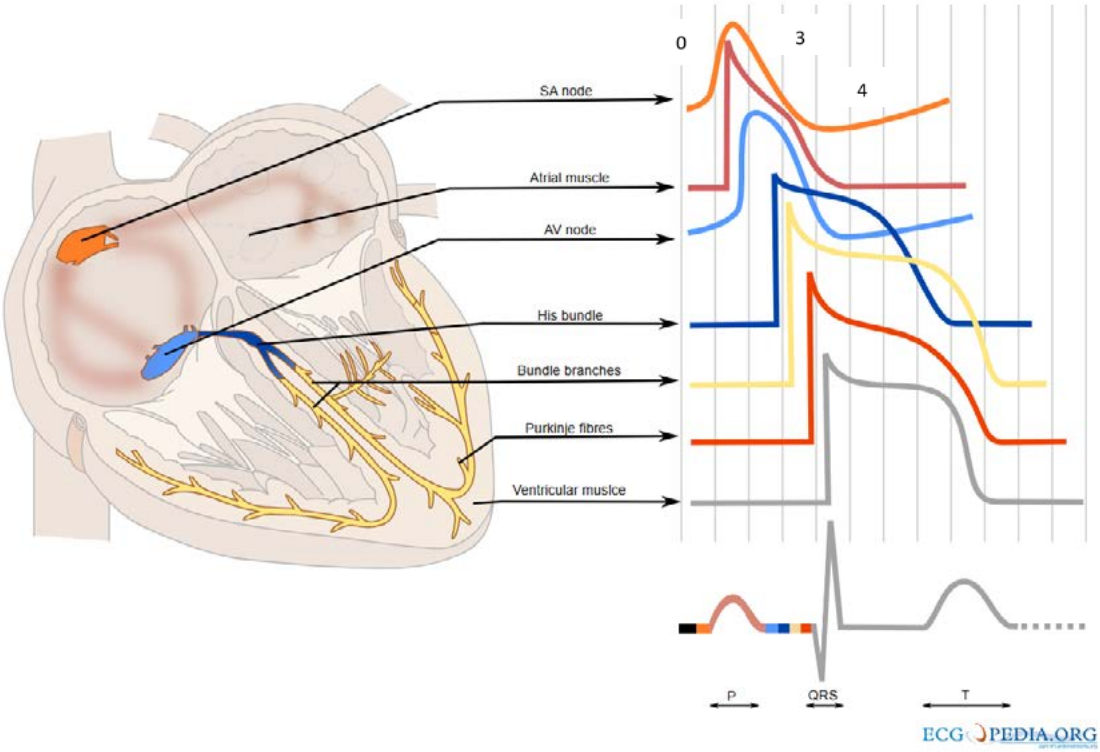

Figure 1: Cardiac APs in different parts of the heart; the phases of the pacemaker APs at the SA node are annotated[4]

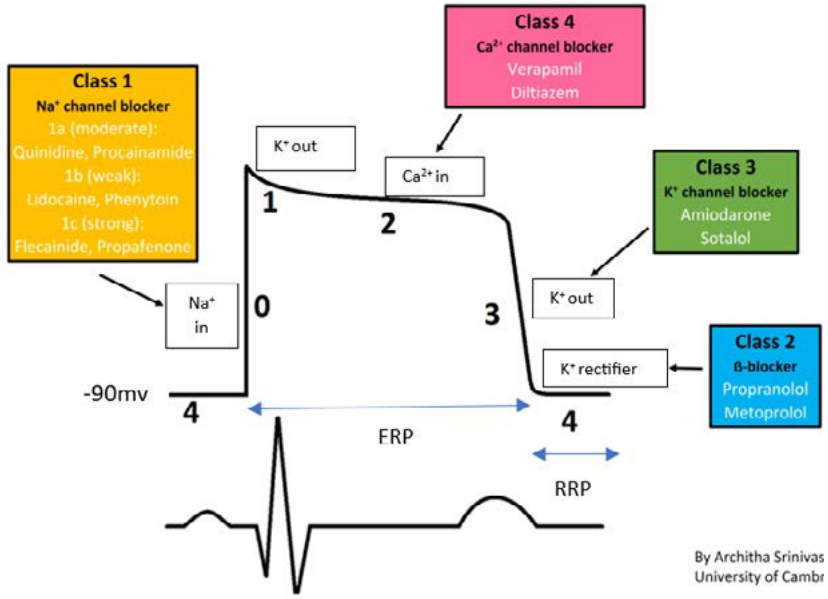

Figure 2: Cardiac AP of a contractile cell and AAD action[6]
ERP – effective refractory period, RRP – relative refractory period

Phase 0 represents rapid depolarisation due to a rapid increase in Na^+ conductance via fast voltage-gated Na^+ ion channels (I_{Na}), resulting in a membrane potential of +30 mV.[1,3,7] The conductance of K^+ decreases.[1] The rate of depolarisation depends on the conduction velocity of the AP.[8] It corresponds with the R wave on the electrocardiogram (ECG).[1,3]

Phase 1 is the "notch" on the AP and represents early transient repolarisation due to the rapid decrease in Na^+ permeability and increased permeability of K^+ ions out of the cell via voltage-gated K^+ channels (I_{to}).[1,3,7] The Na^+ ion channels are in an inactivated state at this time and only enter the active state after repolarisation.[8]

Phase 2 represents the plateau phase and corresponds with the ST segment on the ECG. Voltage-gated L-type Ca^{2+} ion channels (I_{CaL}) open and Ca^{2+} enters the cell during this phase, maintaining depolarisation.[1,3] The Ca^{2+} entering the cell is balanced by K^+ efflux (I_{Ks} and I_{Kr} – see below).[7] The conductance of Na^+ slowly declines.[3] In pathophysiological states, phase 2 of the AP can be prolonged due to continued Na^+ inflow via late Na^+ conductance channels (I_{NaL}).[8] Class Id agents specifically target this channel.[9]

Phase 3 represents the repolarisation phase due to K^+ efflux out of the cell and corresponds with the T wave on the ECG. K^+ efflux occurs via voltage-gated slow delayed rectifier currents (I_{Ks}) and hERG rapid delayed rectifier current K^+ channels (I_{Kr}).[10] Na^+ channels remain closed until a threshold of -65 mV is reached (phase 2). No impulses can be conducted during this time regardless of the strength (effective refractory period - ERP). Once the RMP falls below -65 mV, impulses may be conducted if sufficiently strong (relative refractory period - RRP).[1]

Phase 4 represents the RMP. Na^+ moves into the cell and K^+ moves out via ATPase-dependent ionic pumps to restore the RMP.[1]

Automated cells can be found in the SA node, as well as atrial conduction pathways, parts of the AV node, and the His-Purkinje system.[1] The SA node has the fastest spontaneous depolarisation rate of the automated cells and determines the heart rate.[2] The maximum negative RMP of the SA node is between -50 mV and -70 mV, which is lower than in contractile cells.[1,2] The phases of the AP in the SA node are shown in Figure 1 (phases 0, 3 and 4).

The SA node AP has an unstable RMP and there is no phase 1 or phase 2.[1] Depolarisation is initiated by the inward flow of Na^+ and K^+ (I_f or funny current) via hyperpolarisation-activated cyclic nucleotide-gated (HCN) ion channels, and this determines the automaticity of the SA node (phase 4).[8] Slow, spontaneous inward Ca^{2+} flow via voltage-gated T-type Ca^{2+} channels (I_{CaT}) determines the upstroke of the AP (phase 0).[2] Depolarisation occurs at a RMP of -60 mV (phase 0) and is produced by opening the voltage-gated L-type Ca^{2+} channels (I_{CaL}).[3] It is less rapid than in contractile cells and does not have a plateau phase.[1] Repolarisation occurs after depolarisation due to the inactivation of Ca^{2+} channels and conductance of K^+ via the inward rectifier current channel (I_{K1}) until the maximum negative RMP is achieved again (phase 3).[2,3,8,10] Na^+ conductance changes very little.[2,3]

Mechanisms of arrhythmogenesis

Arrhythmias can occur because of impulse generation or conduction problems, and may be classified as bradyarrhythmias or tachyarrhythmias.[8] Bradyarrhythmias arise from the lack of generation of APs from the SA node or impaired conduction from the atria to the ventricles via the AV node or bundle of His.[8] Tachyarrhythmias can occur due to enhanced automaticity, triggered automaticity, or the reentry phenomenon.[8] Transmural dispersion of repolarisation (TDR) can also predispose to arrhythmia development.[8]

Enhanced automaticity may be normal resulting from vagolytic medication, β-adrenergic stimulation, mechanical stretch, or hypokalaemia.[8] This causes an increase in the upslope of phase

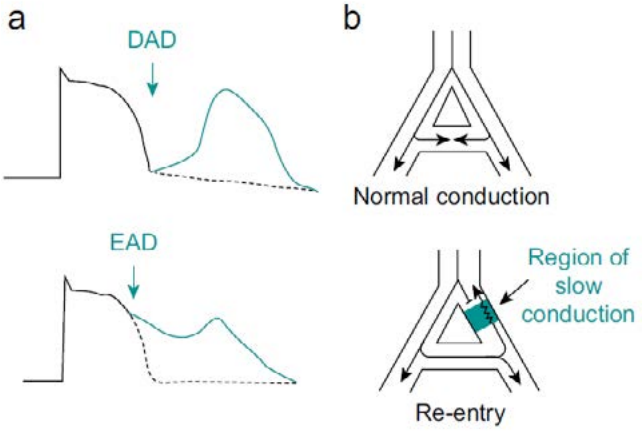

Figure 3: Triggered automaticity and the reentry phenomenon[8]

4 of the pacemaker potential in the SA node, stimulating a faster heart rate.[8] However, enhanced abnormal automaticity occurs when injured myocytes other than in the SA node partially depolarise to a RMP between -60 mV and -40 mV, causing spontaneous depolarisation and ectopic atrial or ventricular tachycardias.[8]

Triggered automaticity may be delayed afterdepolarisations (DAD) or early afterdepolarisations (EAD) resulting from the initiation of a premature AP before the previous beat is complete (Figure 3a).[8] DADs occur during phase 4 of the AP due to an intracellular Ca^{2+} ion overload, which upregulates the Na^+/Ca^{2+} exchanger, bringing the membrane to a threshold potential and triggering a premature contraction.[8] Ca^{2+} overload can be caused by adrenergic stimulation, digoxin toxicity, or myocardial ischaemia.[8]

EADs occur during phase 3, prolonging the AP.[8] This is caused by Na^+ and Ca^{2+} movement into cells and less K^+ efflux out of cells.[8] Drugs or pathologies that inhibit K^+ channels can result in prolonged APs that manifest as a prolonged QT interval.[8] An important clinical consequence of EADs is the development of *torsade de pointes* ventricular tachycardia (VT).[8]

The reentry phenomenon occurs in regions of the heart where there is a structural (accessory pathway) or functional (depolarised from ischaemia) unidirectional block to conduction (Figure 3b).[8] Diseased regions slow conduction velocity and cannot propagate conduction orthograde, but APs can be conducted in a retrograde fashion when Na^+ channels are depolarised outside the ERP.[11] This creates a circular pathway of high-frequency impulses that can be propagated throughout the heart.[11] Pharmacological management that treats the reentry phenomena alters either the timing of conduction or the length of the ERP.[11] AV nodal blocking agents, such as calcium-channel blockers, adenosine, and β-blockers are effective at terminating supraventricular tachycardias (SVTs) involving reentry circuits.[11]

Repolarisation times differ in different regions of the heart resulting in varying durations of APs.[8] These differences are due to intrinsic differences between cell types (e.g. epicardial, endocardial, and M cells) and different ion channel distributions.[8] Drugs that prolong the QT interval or the presence of abnormal tissue preferentially prolong APs in the M cells where the APs are already longer.[8] This increases TDR, predisposing to EADs or reentry circuits that can cause arrhythmias.[8] Increased TDR in patients with long QT syndrome predisposes the development of *torsade de pointes* VT.[8]

Drugs that prolong the QT interval are shown in Table I. Phenylephrine and metaraminol do not affect the QT interval and are safe adrenergic agents to use.[8] Ondansetron has been used safely, although other 5-HT3 antagonists should be avoided.[8]

Table I: Drugs that prolong the QT interval[1,8]

Class of drug	Examples
Adrenergic drugs	Adrenalin, noradrenalin, dopamine, dobutamine, salbutamol, ephedrine
Antiarrhythmic drugs	Quinidine, procainamide, sotalol, amiodarone, ibutilide, dofetilide, isradipine
Antibiotics	Azithromycin, clarithromycin, erythromycin, moxifloxacin, ofloxacin, trimethoprim, sulfamethoxazole
Antifungals	Ketoconazole, fluconazole, itraconazole
Antiemetics	Chlorpromazine, droperidol, domperidone, metoclopramide
Antihistamines	Terfenadine, astemizole
Antipsychotics	Haloperidol, risperidone, clozapine
Anticholinergic agents	Atropine, glycopyrrolate, neostigmine-glycopyrrolate combination
Intravenous anaesthetic agents	Ketamine
Neuromuscular blocking agents	Pancuronium, suxamethonium
Opioids	Methadone, sufentanil
Chemotherapeutics & immunosuppressants	Tamoxifen, tacrolimus
Oxytocic agents	Oxytocin

The mechanisms of arrhythmia generation in the cardiac myocyte cells and the pacemaker cells are summarised in Figure 4.

Ionic changes in arrhythmias

Autonomic nervous system effects alter the permeability of ion channels, resulting in physiological effects.[3] Sympathetic nervous system stimulation leads to the opening of HCN channels with the increased inwards Na^+ and K^+ inflow via the I_f current.[8] Phase 4 of the pacemaker AP is steepened and Ca^{2+} simultaneously enters into cells via I_{CaL}, predisposing to arrhythmias caused by triggered automaticity.[3,8] Conversely, parasympathetic stimulation results in hyperpolarisation of the cell membrane by increased permeability to K^+, inhibiting cardiac activity.[3]

The I_{CaL} channels are predominant in the heart and open when the membrane is depolarised to -10 mV (phase 0); they are also responsible for the maintenance of the plateau phase (phase 2) of the cardiac AP.[3,8] Ca^{2+} channel antagonists block I_{CaL} channels.[3] Verapamil and diltiazem block open and inactivated Ca^{2+} channels and cause a use-dependent block of conduction in pacemaker cells with Ca^{2+}-dependent APs.[5] Dihydropyridines (e.g. nifedipine or amlodipine) block open Ca^{2+} channels.

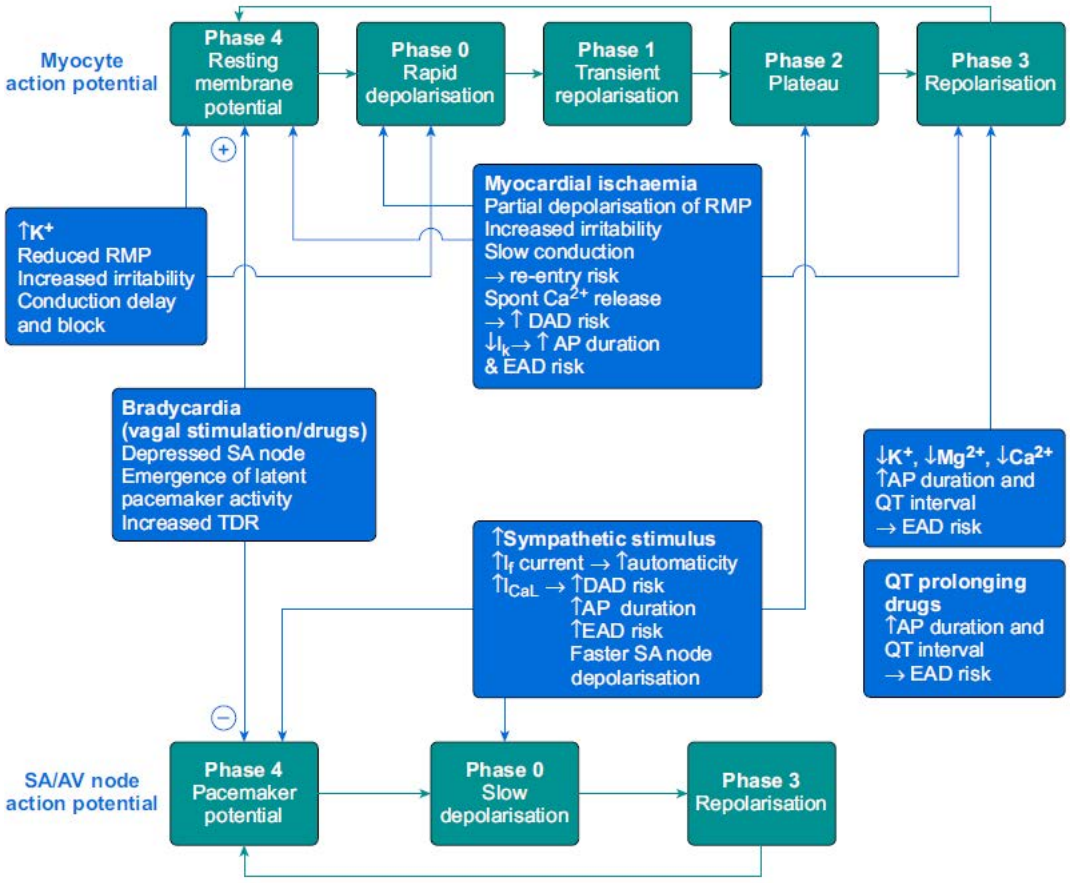

Figure 4: Mechanisms of arrhythmia generation (reproduced with permission)[8]

Catecholamines increase the activation of the I_{CaL} channels via β-stimulation of membrane adenylyl cyclase and increase intracellular cyclic adenosine monophosphate (AMP) production, thereby increasing cardiac activity.[3] The I_{CaT} channels are not affected by catecholamines as they open more briefly at a negative membrane potential (-40 to -70 mV).[3]

Electrolyte disturbances can cause numerous changes at the ionic level of the cell membrane and induce several arrhythmias. Hypokalaemia hyperpolarises the RMP, decreasing membrane excitability, depressing automaticity and causing AV block.[8] K^+ < 2.5 mmol/L inhibits delayed rectifier K^+ channels (I_{Kr}), resulting in a prolongation of the AP and delayed repolarisation.[12] The ERP is prolonged at a time when cardiac tissue is increasingly excitable with an increased risk of developing afterdepolarisations (both EADs and DADs).[8,12] Atrial fibrillation (AF) and atrial flutter are common arrhythmias associated with hypokalaemia.[8]

Hyperkalaemia results in increased membrane permeability to K^+ ions via I_{Kr} and I_{K1} channels, accelerating repolarisation and resulting in a shortening of the AP duration and the refractory period.[8,12] However, as K^+ levels continue to rise (K^+ > 7 mmol/L), the RMP becomes partly depolarised, decreasing excitability and inducing refractoriness, prolonging the ERP.[8] The conduction velocity slows and the slope of phase 0 decreases as the number of Na^+ channels available for depolarisation are reduced.[8] Severe hyperkalaemia is associated with conduction blocks, including atypical bundle branch blocks, intraventricular conduction delays, idioventricular rhythms, asystole, VT, and ventricular fibrillation (VF).[8,12]

Hypocalcaemia (ionised Ca^{2+} < 1.17 mmol/L) can exacerbate the arrhythmogenic effects of hypokalaemia.[8] Phase 2 is prolonged due to a slow increase in Ca^{2+} concentration, thus causing a prolonged AP duration and prolonged ERP.[12] EADs can develop that predispose to *torsade de pointes* VT.[8] Hypercalcaemia (ionised Ca^{2+} > 1.4 mmol/L) shortens phase 2, thus shortening the AP duration and ERP.[12] Elevated Ca^{2+} levels have a stabilising effect on the membrane with limited clinical effects.[8,12]

Hypomagnesaemia (< 0.74 mmol/L) depolarises the membrane due to a decrease in the Na^+/K^+-ATPase pump activity.[8] This slows depolarisation and decreases outward K^+ current flow, resulting in a prolonged QT interval, which increases the risk of ventricular ectopy and *torsade de pointes* VT.[8] Hypermagnesemia, if severe (> 4 mmol/L), can act as a calcium antagonist and depress AV and intraventricular conduction, which may cause bradycardia, hypotension, and conduction defects.[8,12] Administration of Mg^{2+} causes the following effects: prolongs SA node recovery time, prolongs ERP, prolongs QRS duration, suppresses triggered activity, and it is an effective treatment of *torsade de pointes* VT.[12]

Pharmacological principles of antiarrhythmic agents

Mechanisms of arrhythmia management (Table II) include the suppression of automaticity, prevention of triggered automaticity, and alterations to conduction velocity and refractoriness of tissue to prevent the reentry phenomena.[10]

Table II: Mechanisms of arrhythmia prevention and management[10]

Mechanism	Effect	Example
Suppression of enhanced automaticity		
Hyperpolarisation of RMP	Increase inward K^+ ion effect during phase 4 of AP	Adenosine
Decrease slope of spontaneous pacemaker cells	Reduce the inward flow of cations during phase 4 of the pacemaker potential	β-blockers (Class II)
Increase threshold potential	Na^+ or Ca^{2+} channel blockade	Class I agents Ca^{2+} channel blocker (Class IV)
Increase AP duration	Block flow of ions via K^+ rectifier channels	Class III agents
Inhibition of triggered automaticity		
DADs prevented by reducing the possibility of the membrane reaching threshold potential	Reduce activity of Ca^{2+} ion channels by reducing Na^+/Ca^{2+} exchanger	Directly: β-blockers (Class II) Indirectly: Ca^{2+} channel blocker (Class IV)
EADs prevented by shortening the AP duration	Effect on ionic channels during phase 3 of AP	β-blockers (Class II), Ca^{2+} channel blockers (Class IV), Na^+ channel blockers (Class Ib)
Inhibition of reentry phenomena		
Increase the ERP	Na^+ channel recovery slowed from an inactivated state Block K^+ rectifier channels	Class Ia & Ic agents Class III
Increase conduction velocity in affected regions	Bind inactivated Na^+ channels with very rapid dissociation causing Na^+ channels to recover rapidly, reducing AP duration	Lignocaine (Class Ib)

Most AADs work on channels that are active or inactive, not those in a resting state (termed user dependency).[10] Thus, agents are more effective during tachycardia or when the RMP is not at a normal level (such as in diseased tissue). With increasing doses, pro-arrhythmogenicity can result due to ion channels in normal tissue being affected.[10]

Classification of antiarrhythmic agents

The simplest classification of AADs is the Singh Vaughan-Williams classification, which divides agents into four classes based on the primary mechanism of action.[1,2] A fifth group is described in some texts.[7]

There are several limitations to this classification system. Some drugs have multiple mechanisms of action and do not fit into one class only.[13] Active drug metabolites may have different mechanisms to the parent drug.[1] Some AADs were not originally included and do not fit into this classification system.[13] AP duration prolongation can occur from multiple ion channel effects, which is not considered.[13] The mechanism of arrhythmogenesis is not taken into account.[13] Classification is based on electrophysiological effects on normal tissue and not diseased tissue or tissue chronically exposed to AADs.[13] The American Heart Association updated the Singh Vaughan-Williams classification in 2018, retaining the four core classes but expanding the classification based on newer and potential AADs and assigning previously unclassified AADs into these classes (Table III).[1,7,9,10,13] Changes to the original classification are italicised in Table III.

The Sicilian Gambit classification system was described in 1991, providing a more holistic approach to AADs from an electrophysiological, electrocardiographic, and clinical perspective.[13] The mechanism of arrhythmogenesis is considered rather than the mechanism of action of the AAD.[13] Novel approaches to the choice of AAD prescription consider the vulnerable electrophysiological parameters present and aim to address this directly.[13]

AADs can also be classified according to their site of action, as described below:[1,2]

- Supraventricular tachyarrhythmias: quinidine, procainamide, disopyramide, propafenone, β-blockers
- Ventricular tachyarrhythmias: lignocaine, mexiletine
- SA node: atropine, isoproterenol
- AV node: digoxin, verapamil, β-blockers, atropine, isoproterenol
- Accessory pathway: β-blockers, amiodarone, disopyramide

The mechanism of action of AADs on the phases of the cardiac and pacemaker APs is schematically shown in Figure 5.[10]

Clinical pharmacology

Most AADs have a pro-arrhythmogenic potential, predominantly from effects on the QT interval.[7] Prolongation of the QT interval can increase the risk of *torsade de pointes* VT.[7] AV block and bradycardia can occur from several AADs as a result of effects on automaticity and conduction velocity.[7]

Other side effects specific to certain AADs can occur. Procainamide can induce reversible systemic lupus erythematosus.[1] Disopyramide can cause anticholinergic effects, including mydriasis, urinary retention, dry skin, thirst, and agitation, limiting the tolerability of this drug.[7] Dronedarone can cause acute fulminant liver failure, requiring transplantation.[1]

Several AADs are commonly used for the management of acute arrhythmias. The clinical pharmacology of selected AADs is described below with doses shown in Table IV.

Table III: Updated Singh Vaughan-Williams classification of AADs[1,7,9,10,13]

Class	Pharmacological target	Electrophysiological effects	AP/ERP duration	ECG effects	Drugs	Clinical applications & mechanisms
HCN channel blockers						
0	*HCN channel modulators*	*Inhibition of I_f and cation inflow, reduced SA node phase 4 pacemaker depolarisation rate*	*0*	*↑ RR intervals*	*Ivabradine*	*HR control in angina and stable cardiac failure*
Voltage-gated Na^+ channel blockers (Ic > Ia > Ib)						
Ia	Block fast I_{Na} in open state, intermediate dissociation kinetics	↓ rate of depolarisation (phase 0), reduced excitability of non-nodal tissue	↑ AP ↑ ERP	↑ PR, ↑ QRS, ↑ QT	Quinidine, procainamide, disopyramide	SVT, AF, VT/VF ↓ reentrant tendency ↓ automaticity
Ib	Block I_{Na} in open state, fast dissociation kinetics	Little effect on phase 0, suppression of phase 4 in pacemaker cells	↓ AP ↓ ERP	↓ QT (slight)	Lignocaine, mexiletine, phenytoin	VT, particularly after MI ↓ reentrant tendency Reduced DADs
Ic	Block I_{Na} in inactivated state, slow dissociation kinetics	Marked ↓ phase 0, slows conduction velocity, reduces excitability	No effect on AP & ERP	↑ PR, ↑ QRS, no effect on QT	Propafenone, flecainide	AF and atrial flutter ↓ reentrant tendency Reduced DADs
Id	*Late Na^+ channel blocker (I_{NaL})*	*Decreased AP recovery time, ↑ refractoriness of Na^+ channels*	*↓ AP* *↓ ERP*	*↓ QT*	*Ranolazine*	*AF treatment & prevention* *Reduction in EADs*
Autonomic modulators						
IIa	Nonselective β-blockers (NS) and selective β1 blockade (S)	Slowed SA node pacemaker rate caused by reduced I_f & I_{CaL}, reduced automaticity (phase 4)	↓ AP ↑ ERP	↑ PR, ↓/0 QT	NS: carvedilol, propranolol S: atenolol, esmolol, bisoprolol, metoprolol	Prevention of SVT Rate control of atrial and ventricular tachyarrhythmias Reduced EADs & DADs
IIb	*Nonselective β-agonist*	*Activate Ca^{2+} entry and sarcoplasmic-mediated Ca^{2+} release*	*↓ AP*	*↓ PR, ↓ RR interval*	*Isoproterenol*	*Ventricular escape rhythm* *Complete AV block*
IIc	*Muscarinic M2 receptor inhibitors*	*Inhibition of M2 receptors at SA node, increased automaticity, ↑ AV conduction*	*↓ AP*	*↓ PR, ↓ RR interval*	*Atropine, glycopyrrolate*	*Symptomatic sinus bradycardia* *Conduction block*
IId	*Muscarinic M2 receptor activators*	*Hyperpolarised SA node & reduced automaticity, reduced conduction* *Digoxin: inhibits Na/K-ATPase pump, ↑ Na^+/$Ca2^+$ intracellularly, prolonging phase 4 & phase 0 of AP*	*↓ AP*	*↑ PR, ↑ RR interval*	*Pilocarpine, carbachol, methacholine* *Digoxin*	*SVT*
IIe	*Adenosine A1 receptor activators*	*Activate inward K rectifier channels, hyperpolarising the SA node & decreasing automaticity; ↓Ca influx via I_{CaL}*	*↓ AP*	*↑ PR, ↑ RR interval*	*Adenosine*	*SVT* *Reduced EADs & DADs*
K^+ channel blockers/openers						
IIIa	Voltage-dependent K^+ channel blockers: NS, rapid K^+ (R, hERG) or ultra-rapid K^+ (UR) current blockers	Block multiple K^+ channel targets resulting in prolonged AP recovery time, ↑ refractory period with ↓ reentrant tendency Amiodarone: sympatholytic, Na^+/Ca^{2+} channel blockade	↑ AP ↑ ERP	NS: ↑ PR, ↑ QRS, ↑ QT R: ↑ QT UR: ↑ QT	NS: amiodarone, dronedarone R: ibutilide, sotalol UR: vernakalant	NS: AF, VT, VF R: VT, WPW associated AF UR: cardioversion of AF
IIIb	*Metabolically dependent K^+ channel blockers*	*Open ATP-sensitive K^+ channels*	*↓ AP recovery time*	*↓ QT*	*Nicorandil, pinacidil*	*Stable angina* *Hypertension (investigational)*
Ca^{2+} handling modulators						
IVa	Surface membrane Ca^{2+} channel blockers: nonselective or I_{CaL}	Decrease the slope of phases 0 & 4 and prolong phase 2 of the cardiac AP, inhibits SA node pacing	↑ AP ↑ ERP	↑ PR	NS: bepridil, falipamil I_{CaL}: verapamil, diltiazem	SVT SVT, rate control AF & atrial flutter Reduced EAD & DAD triggered arrhythmias

IVb	*Intracellular Ca^{2+} channel blockers*	*Reduced sarcoplasmic Ca^{2+} release*	*0/↑ AP*	*↑ PR, ↑ QRS, ↑ QT*	*Propafenone, flecainide*	*Catecholaminergic Polymorphic VT Reduced EAD & DAD triggered arrhythmias*
V	*Mechanosensitive channel blockers*	*Intracellular Ca^{2+} signalling*			*Drugs under investigation*	*Reduced EAD & DAD triggered arrhythmias*
VI	*Gap junction channel blockers*	*Reduced cell-cell coupling and AP propagation*			*Drugs under investigation*	*Reduced conduction*
VII	*Upstream target modulators*	*Electrophysiological and structural (fibrotic, hypertrophic, or inflammatory) remodelling*			*ACEi, ARBs Statins, omega-3 fatty acids*	*Reduce AP conduction and ↑ reentry tendency*

AF – atrial fibrillation, AP – action potential, AV – atrioventricular, DAD – delayed afterdepolarisations, EAD – early afterdepolarisations, ERP – effective refractory period, SVT – supraventricular tachycardia, VT – ventricular tachycardia, VF – ventricular fibrillation, WPW – Wolff-Parkinson-White, 0 - no effect

Lignocaine[1,10]

Lignocaine is a Class Ib agent and blocks fast-conducting Na^+ channels in the AV node and conducting tissue. It is the first-line agent for the treatment of VT and VF and is ineffective for atrial arrhythmias.

Lignocaine undergoes hepatic metabolism and drug concentration can be affected by other drugs that affect hepatic cytochrome oxidase metabolism, by low cardiac output states, or hepatic dysfunction. Lignocaine has a rapid onset of action with a wide therapeutic index. In therapeutic doses, it has a minimal effect on cardiac contractility and vascular tone and does not affect the QRS duration, ERP, and QT interval. The main adverse effect is central nervous system excitation, which can occur in high doses or with prolonged infusions. This should be managed as local anaesthetic systemic toxicity and should be treated with Intralipid administration.

β-blockers[1,7,10,14]

β-blockers are Class IIa agents and can be selective or nonselective β-adrenergic antagonists. They can be used for the treatment of supraventricular tachyarrhythmias, ventricular arrhythmias (VT, polymorphic VT or VF), or for rate control in AF, atrial flutter, or orthodromic Wolff-Parkinson-White (WPW) syndrome.

β_1-receptor antagonism decreases automaticity in the heart and slows down conduction in the SA and AV nodes and ventricles. The decreased heart rate reduces myocardial oxygen demand, which could be beneficial in patients with coronary artery disease.

Side effects of β-blockers include myocardial depression, bronchospasm, AV block, bradycardia, and worsening of peripheral vascular symptoms. β_1-selective blockers (bisoprolol, esmolol, atenolol, metoprolol) may limit the adverse effects of bronchial reactivity and peripheral vasculature.

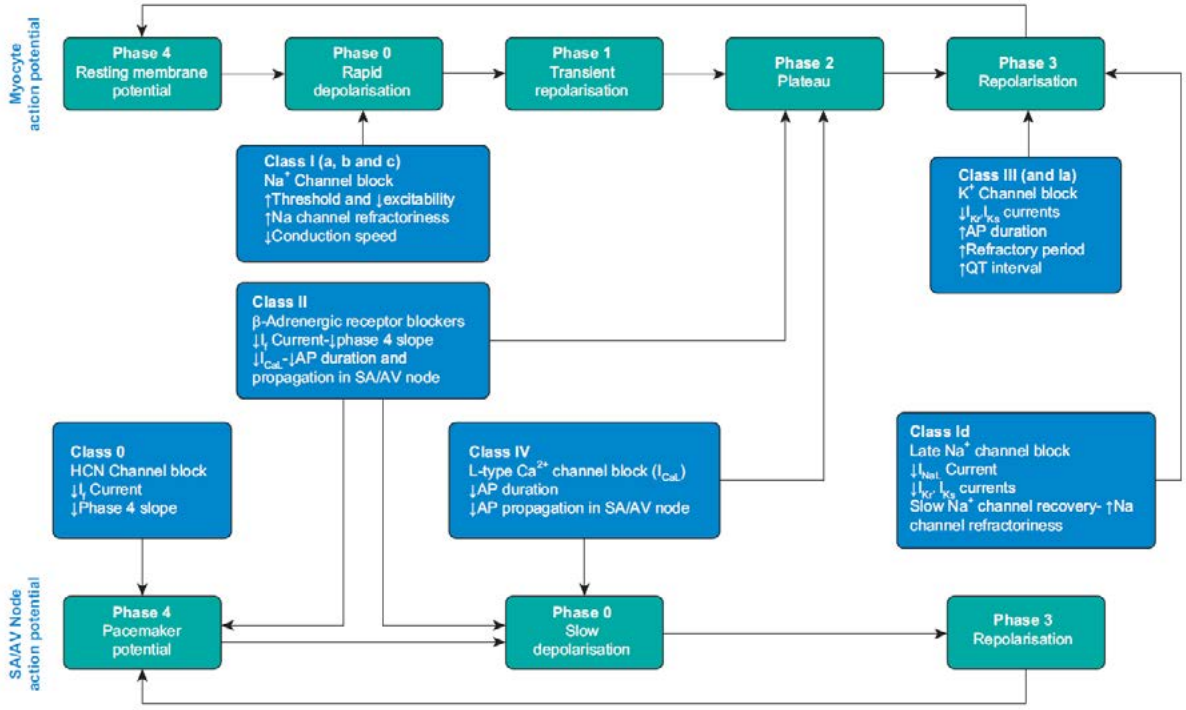

Figure 5: Schematic diagram of the mechanism of action of AADs (reproduced with permission)[10]

Esmolol is an ultra-short-acting β_1-selective blocker with negative chronotropic, dromotropic, and inotropic effects. It has a distribution half-life of two minutes and a clinical effect lasting 20 minutes. Metabolism occurs by hydrolysis by red cell esterase, its metabolites are inactive and are renally excreted. It is a water-soluble drug and does not cross the placenta or the blood-brain barrier. Propranolol is a long-acting nonselective β-blocker that is highly fat-soluble with central effects. It has a half-life of 3–4 hours and undergoes an extensive first pass effect (oral administration). It can be used during the management of thyroid storm, provided the patient does not exhibit features of cardiac failure. Sotalol is a unique nonselective β-blocker with Class III effects. It can prolong the QT interval and may be pro-arrhythmogenic.

Digoxin[1,7,10,15]

Digoxin inhibits the Na^+/K^+ -ATPase pump increasing the intracellular concentration of Na^+. This reduces the 3 Na^+/Ca^{2+} exchanger, increasing intracellular Ca^{2+} and causing positive inotropy. Digoxin also suppresses the SA node (decreased phase 4) and delays conduction via the AV node making it negatively chronotropic and dromotropic. The vagolytic effect is caused by AV node refractoriness decreased by Ca^{2+} flow and increased K^+ flow in the AV node and atria.

Digoxin can be used in patients with AF with impaired cardiac function, reentrant arrhythmias involving the AV node, and control of rapid ventricular response rate in AF. Digoxin is contraindicated in patients with heart block, hypertrophic obstructive cardiomyopathy, and preexcitation syndromes (e.g. WPW). Slow AV conduction can result in rapid conduction via an accessory pathway in WPW that can lead to cardiovascular collapse.

Digoxin has a long half-life of 36 hours and is renally excreted. It has a narrow therapeutic index and should be monitored in patients with renal dysfunction, low body mass index, or in elderly patients. Toxicity occurs at plasma levels > 2.5 ng/ml and can be precipitated by electrolyte abnormalities (hypercalcaemia, hypokalaemia, or hypomagnesaemia), hypoxia, hypoventilation, or in combination with other AADs. Toxicity can result in nausea, vomiting, visual abnormalities, delirium, and convulsions. Cardiac effects of toxicity may manifest early with bradycardia; however, ventricular bigeminy or trigeminy, VT, paroxysmal atrial tachycardia (with variable blocks), or VF can occur. Digoxin toxicity is treated with lignocaine (tachyarrhythmias), atropine (bradyarrhythmias), or a pacemaker can be temporarily used. Hypokalaemia must be urgently corrected. Immunotherapy with anti-digoxin antibody fragments can be considered.

Adenosine[1,7,10]

Adenosine acts on adenosine-sensitive K^+ channels, increasing conductance and shortening the AP. It also decreases Ca^{2+} conductance resulting in a hyperpolarised membrane at the SA and AV nodes, thus decreasing automaticity and slowing conduction via the AV node. It is negatively chronotropic and dromotropic. It is used in AV reentry tachycardias and orthodromic WPW syndrome. It can be used to diagnose or terminate SVTs and to unmask atrial flutter or AF. As there are no adenosine-sensitive K^+ channels in the ventricles, it is not effective for ventricular arrhythmias.

Adenosine has a short half-life of 10 seconds as it is rapidly taken up into red blood cells. It should be avoided in patients with a heart block. It can cause flushing, chest pain, AV block, and transient asystole. It may occasionally cause AF or bronchospasm.

Amiodarone[1,7,10]

Amiodarone is unique among the AADs as it has activity across all the classes. It predominantly inhibits nonselective K^+ channel conductance (I_{Kr} and I_{Ks}), but also inhibits fast Na^+ channels and Ca^{2+} channels, and blocks β-adrenergic blockers in the SA and AV nodes, accessory pathways and ventricular tissue. It can be used for both atrial (SVT, AF, flutter) and ventricular (monomorphic or polymorphic VT) arrhythmias, as well as arrhythmias caused by accessory pathways. It forms part of the cardiac arrest algorithm for VF or pulseless VT unresponsive to defibrillation.

An intravenous loading dose is needed to achieve a steady-state concentration. It is highly lipid soluble and protein bound with a long elimination half-life of 29 days. It is metabolised in the liver with an active metabolite as effective as the parent drug. Amiodarone can prolong the QT interval and should be used with caution in combination with other drugs that prolong the QT interval (Table I). Drugs that potentiate the hepatic cytochromes that metabolise amiodarone can affect its levels. Amiodarone can also inhibit cytochromes causing increased levels of warfarin and digoxin.

Amiodarone is a negative inotrope and vasodilator. It can result in bradycardia and hypotension that can be potentiated by coadministration with other AADs. Acute pulmonary toxicity is a life-threatening side effect resembling acute respiratory distress syndrome. Amiodarone can also be pro-arrhythmogenic causing VT, VF or *torsade de pointes* , although the potential for this is low. Chronic side effects include chronic pulmonary toxicity, hepatic dysfunction, ocular toxicity (corneal opacities, photosensitivity, optic neuritis, decreased visual acuity), hyper- or hypothyroidism, and peripheral neuropathy.

Vernakalant[10]

Although classified as a Class III AAD, vernakalant acts on Na^+ and delayed K^+ rectifier channels, prolonging the ERP and AP. The QT interval is marginally prolonged and it does not increase the risk of *torsade de pointes*. Vernakalant can be used as pharmacological cardioversion in acute AF as it is atrium-specific in action. Bradycardia and hypotension are side effects.

Sotalol[10]

Sotalol is a selective K^+ channel blocker acting at the hERG K^+ channel. It is used for the management of VT and the maintenance of sinus rhythm in AF. There is a risk of developing *torsade de pointes* due to its prolongation of the QT interval, and it can cause nonselective β-blockade.

Calcium-channel blockers[1,7,10]

Non-dihydropyridine Ca^{2+} channel blockers have antiarrhythmic effects. Verapamil is classified as a phenylalkylamine and diltiazem is a benzothiazepine. Their effects are exerted by blockade of the L-type Ca^{2+} channels in the SA and AV nodes, depressing automaticity and decreasing conduction speed. Verapamil has a limited effect on AV conduction at low heart rates.

Ca^{2+} channel blockers are effective at reducing the ventricular response rate in AF or atrial flutter and for the management of reentry tachycardias. Ca^{2+} channel blockers are contraindicated in preexcitation syndromes as they do not suppress conduction via accessory pathways; they should be used with caution in patients with heart failure as they can cause myocardial depression. They are not effective in managing ventricular arrhythmias.

Verapamil can cause side effects including AV block, bradycardia, oedema, and constipation, while diltiazem can cause oedema, headaches, and dizziness.

Magnesium[10,12]

The antiarrhythmic mechanism of magnesium may be related to the membrane stabilising properties due to Ca^{2+} and K^{+} channel blockade. It also suppresses triggered activity. It does not affect the QT interval. Magnesium is indicated for the prevention or treatment of *torsade de pointes*, control of ventricular rate response in AF, and the management of arrhythmias associated with digoxin toxicity.

The doses of commonly used AADs are shown in Table IV.

Table IV: Dosages of commonly used intravenous AADs in adults[1,10,14]

Drug	Dose
Adenosine	6 mg as a rapid bolus 6–12 mg; repeat if needed
Amiodarone	Cardiac arrest: first dose 300 mg bolus, second dose 150 mg bolus 300 mg loading dose followed by 900 mg as an infusion over 24 hours
Atropine	600 µg bolus, up to a maximum of 3 mg
Digoxin	0.25–0.5 mg bolus or 10–20 µg/kg Maximum 1 mg per 24 hours
Diltiazem	20 mg
Esmolol	250–500 µg/kg bolus Infusion: 50–200 µg/kg/min
Lignocaine	Cardiac arrest: first dose 1–1.5 mg/kg, second dose 0.5–0.75 mg/kg Bolus: 2 mg/kg followed by infusion of 1–4 mg/min
Magnesium	1–2 g magnesium sulphate
Propranolol	1 mg increments up to 5–10 mg
Vernakalant	3 mg/kg bolus, repeat dose of 2 mg/kg after 10 minutes
Verapamil	75–150 µg/kg over 1–3 minutes or 5–10 mg Infusion: 5 µg/kg/min

Management of perioperative arrhythmias

The precipitant of the arrhythmia must be determined, and the risk versus the benefit of therapy must be considered before initiation an AAD. Unstable tachyarrhythmias must be treated with synchronised cardioversion with concomitant amiodarone administration.[7] Amiodarone has a low pro-arrhythmogenic potential and it is effective in managing both atrial and ventricular tachyarrhythmias.[7]

AF is a common arrhythmia in the perioperative period with the majority of episodes being self-limiting. Cardioversion should be reserved for AF with haemodynamic instability. β-blockers are the first-line agent for haemodynamically stable patients.[7] Digoxin in combination with β-blockers or Ca^{2+} channel blockers can be considered if the patient has impaired ventricular function.[7] Amiodarone or vernakalant can be considered for pharmacological cardioversion of acute AF to restore sinus rhythm when electrical cardioversion is not indicated.[7]

Conclusion

AADs can be classified using the updated Singh Vaughan-Williams classification based on the mechanism of action of each drug. Potential uses and side effects can be determined from the electrophysiological effects of each drug. In the perioperative period, patients on chronic AADs may be encountered or commonly used AADs may be needed for the management of perioperative arrhythmias. An understanding of the physiology of cardiac conduction, the mechanisms of arrhythmogenesis, and the classification of AADs enables the rational use of therapy and recognition of adverse effects.

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References

1. Hosking CA, Dippenaar JM. Antiarrhythmic agents. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. China: Everbest Printers; 2019. p. 398-419.
2. Peck TE, Hill SA, Williams M. Pharmacology for anaesthesia and intensive care. 3rd ed. United Kingdom: Cambridge University Press; 2008. https://doi.org/10.1017/CBO9780511722172.
3. Kam P, Power I. Principles of physiology for the anaesthetist. 2nd ed. New York: Oxford University Press; 2008.
4. ecgpedia.org [Internet]. Shapes of the cardiac action potential in the heart. Wikimedia Commons; 2011. Available from: https://commons.wikimedia.org/wiki/File:Shapes_of_the_cardiac_action_potential_in_the_heart.svg. Accessed 29 August 2023.
5. Grant AO. Cardiac ion channels. Circ Arrhythm Electrophysiol. 2009;2(2):185-94. https://doi.org/10.1161/CIRCEP.108.789081.
6. Srinivasan A. Drugs affecting the cardiac action potential [Internet]. In: commons.wikimedia.org. University of Cambridge; 2016. Available from: https://commons.wikimedia.org/wiki/File:Cardiac_action_potential.png. Accessed 28 August 2023.
7. King GS, Goyal A, Grigorova Y, Hashmi MF. Antiarrhythmic medications [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 February 19]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482322/. Accessed 29 August 2023.
8. Kim CJ, Lever N, Cooper JO. Antiarrhythmic drugs and anaesthesia: part 1. mechanisms of cardiac arrhythmias. BJA Educ. 2023;23(1):8-16. https://doi.org/10.1016/j.bjae.2022.11.001.
9. Lei M, Wu L, Terrar DA, Huang CL-H. Modernized classification of cardiac antiarrhythmic drugs. Circulation. 2018;138(17):1879-96. https://doi.org/10.1161/CIRCULATIONAHA.118.035455.
10. Kim CJ, Lever N, Cooper JO. Antiarrhythmic drugs and anaesthesia. Part 2: pharmacotherapy. BJA Educ. 2023;23(2):52-60. https://doi.org/10.1016/j.bjae.2022.11.005.

11. Klabunde RE. Cardiology physiology concepts: reentry [Internet]. 2022. Available from: https://cvphysiology.com/arrhythmias/a008c. Accessed 26 August 2023.
12. El-Sherif N, Turitto G. Electrolyte disorders and arrhythmogenesis. Cardiol J. 2011;18(3):233-45.
13. Dan G-A, Martinez-Rubio A, Agewall S, et al. Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). Europace. 2018;20(5):731-2an. https://doi.org/10.1093/europace/eux373.
14. Nienaber LN, Biccard BM. Autonomic nervous system. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. China: Everbest Printers; 2019. p. 161-216.
15. Royse C, Radford HM, Milner A. Organ failure. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. China: Everbest Printers; 2019. p. 217-46.

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FCA REFRESHER COURSE

Physical principles that enable cardiac output monitoring

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Introduction

The primary homeostatic role of the cardiovascular system is to ensure that all the metabolic demands of the tissues are met. This is achieved by the delivery of oxygen and nutrients to the tissues with simultaneous removal of waste products of metabolism and cellular respiration. The delivery of oxygen to the tissues (DO_2) is dependent on cardiac output (CO) and arterial oxygen content (CaO_2) and can be calculated with the following equation:[1]

$$DO_2 = CaO_2 \times CO$$

CaO_2 in turn is dependent on the haemoglobin concentration (Hb), haemoglobin oxygen saturation (SpO_2), and partial pressure of oxygen (PO_2) in arterial blood and can be calculated with the following equation:[1]

$$CaO_2 = (1.39 \times Hb \times SpO_2 / 100) + (0.003 \times PO_2)$$

Continuous non-invasive monitoring of SpO_2 can be achieved with photoplethysmography using the modified Beer-Lambert's law, while PO_2 and Hb can be measured by blood gas analysis, all of which is beyond the scope of this review.[2] However, in the absence of anaemia and hypoxaemia, DO_2 is dependent on CO. CO is defined as the volume of blood ejected from the right or left ventricle per unit of time and is therefore the product of HR and stroke volume (SV):[3]

$$CO = HR \times SV$$

CO monitoring has become commonplace in the management of critically ill patients, those undergoing anaesthesia for major surgical procedures, and patients with limited cardiopulmonary reserve.[4] Numerous methods have been used to measure CO, all of which derive a value from an inference of SV or flow, both of which cannot be measured directly. For this reason, each of the CO monitoring techniques is coupled with potential sources of error and limitations to their use. Despite this, the clinical necessity for an ideal CO monitor is strongly asserted by a wealth of literature suggesting that therapies should be directed at improving DO_2 with goal-directed interventions, whilst liberal fluid therapies may be harmful.[5]

This review aims to explain the physical principles that enable each of the CO monitoring techniques. An appreciation of the physics behind these techniques is essential to understanding their strengths and limitations in clinical application.

The ideal CO monitor[6]

The ideal CO monitor should be:

- non-invasive or minimally invasive without the need for calibration;
- quick and easy to set up;
- safe to use;
- operator independent with minimal specialised training required;
- appropriate for use in a wide variety of clinical settings;
- appropriate for use in adult and paediatric patients;
- appropriate for use in intubated and non-intubated patients; and
- provide real-time, continuous, accurate and reproducible data that are reliable under different physiological conditions.

No single CO monitor is presently able to satisfy all the clinical criteria above.

Types of CO monitors[7]

Each CO monitoring technique can be classified as one of the following:

- Invasive techniques: These techniques make use of a central line and arterial line or a pulmonary artery flotation catheter (PAFC)/Swan-Ganz catheter. Invasive techniques include the Fick principle, dye dilution, lithium dilution, thermodilution, pressure waveform analysis, and pulse pressure contour analysis.
- Minimally invasive techniques: These techniques make use of transoesophageal ultrasound and the Doppler effect.
- Non-invasive techniques: These techniques include bioimpedance, bioreactance, and tonometry, which make use of the application of electrodes or cuffs to the surface of the body.

A variety of physical principles have been exploited in the calculation of CO using the above techniques. These principles will be elaborated on below.

Invasive techniques

Fick principle

The Fick principle, developed by Adolf Eugen Fick in the late 1800s, asserts that the total amount of a substance that is taken up or excreted by an organ is equivalent to the product of the blood flow through that organ and the difference in the arterial and venous concentrations of the substance in the blood supplying and leaving that organ respectively.[8] If one considers the lungs as the organ of interest, oxygen can be considered as a "substance" that is completely added, from the alveoli to the blood as it moves through the pulmonary circulation. Hence, if the pulmonary arterial oxygen content (CvO_2) as well as the systemic arterial oxygen content of blood (CaO_2) is known, the pulmonary blood flow (PBF) can be calculated provided the amount of oxygen taken up by the blood through the alveoli (VO_2) is known.

$$PBF = VO_2 / (CaO_2 - CvO_2)$$

Since the entire right ventricular CO passes through the pulmonary circulation, it can be assumed that the right ventricular CO is equal to the PBF. The pulmonary and systemic circulations are arranged in series. Consequently, it is assumed that the left ventricular CO is equivalent to the right ventricular CO and therefore, systemic CO can be calculated.

This method of CO monitoring requires the patient to breathe 100% oxygen from a closed system incorporating a carbon dioxide absorber and a spirometer that contains a known amount of oxygen over a period of one minute. Oxygen readily diffuses across the alveolar-capillary barrier along a concentration gradient. The rate of diffusion (V_{gas}) has been described by Fick's law[9] and is directly proportional to the partial pressure gradient ($P_1 - P_2$) across the barrier and the surface area available for diffusion (A), while it is inversely proportional to the thickness of the alveolar-capillary membrane (T).[9]

$$V_{gas} = D_{Constant} \times (A / T) \times (P_1 - P_2)$$

After one minute, the amount of oxygen drawn through the spirometer is measured as the VO_2. Further placement of a PAFC is required so that CvO_2 can be calculated from mixed venous blood gas analysis while CaO_2 is calculated from peripheral arterial blood gas analysis.

Dye dilution technique

This method of CO calculation requires the injection of a marker or dye (usually indocyanine green) into the blood.[2] The dye is injected into a central vein or the pulmonary artery through a central venous catheter or PAFC. The dye should mix completely with the blood, circulate, and remain in the intravascular space while being minimally metabolised. CO can be calculated if the change in concentration of the dye, at a point downstream of the initial injection point (usually a peripheral arterial line) can be measured and plotted against time.[2] An optical dye detector is usually utilised at the arterial line.

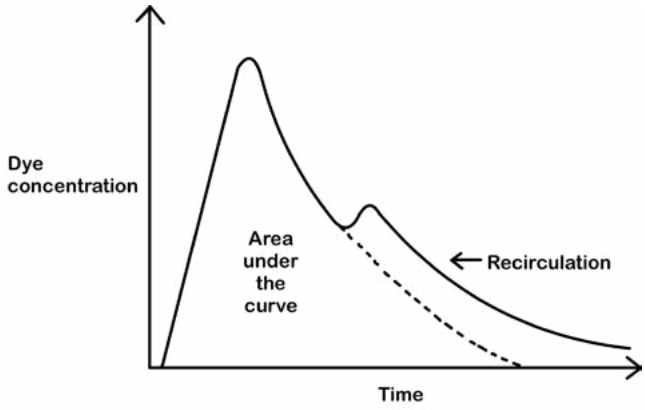

Figure 1: A graph depicting a washout curve

The resulting graph of dye concentration plotted against time is termed a washout curve with an initial peak concentration reached rapidly after dye injection with a subsequent exponential decrement in dye concentration as it is diluted and "washed out" (Figure 1).[2] The dye travels at a range of velocities from the point of injection towards the detector due to laminar flow.[2] This results in a slightly delayed, rounded peak to the plasma concentration at the detection site after injection.[2] Finally, the concentration of dye decays exponentially and predictably. However, some dye recirculates and will result in a second peak due to fast-moving dye. The rate at which dye is "washed out" is directly proportional to the flow rate (CO) and the concentration of dye injected.[2]

The Stewart-Hamilton equation can be used to calculate the CO based on the following mathematic principles:

- The volume of a dye or marker is equal to the mass of the dye divided by the concentration.
- If concentration is measured over time, the rate of change of volume (flow) can be calculated.
- Hence, CO (flow) can be calculated by dividing the mass (amount) of dye injected by the mean concentration of dye over time (area under the exponential decay curve) using the following formula:[2]
  - CO = amount of dye injected / area under the graph

Lithium chloride dilution technique

Calculating CO using lithium chloride as a marker makes use of the same dilution technique described in the dye dilution method above. Lithium chloride is an ion that is not normally present in plasma, so only a small dose of this marker is necessary to produce a reliable washout curve.[2] Secondly, the small dose of the marker reduces the risk of toxicity or an adverse reaction.[2] Lithium chloride is not a dye and a different method of concentration sampling is necessary at the arterial line. Following a bolus of lithium chloride injected into a central vein, the resulting lithium concentration-time curve is recorded by drawing a blood sample past an electrochemical lithium-ion detector attached to the patient's peripheral arterial line.[2] CO can be calculated from the known dose of lithium chloride injected and the area under the graph generated using the Stewart-Hamilton equation.[2]

Thermodilution technique

Dye and lithium chloride dilution techniques are confounded by the recirculation of the marker that needs to be excluded by the logarithmic transformation of concentration measurements and extrapolation of the exponential decay curve to the baseline of the graph. This confounder is avoided by making use of the thermodilution method of CO calculation. Traditionally, a PAFC is placed through the right internal jugular vein and advanced through the right atrium, tricuspid valve, right ventricle, and finally floated through the right ventricular outflow tract to settle in the pulmonary artery.[2] A measurement of 10–15 ml cold saline at 0 °C is injected into the proximal port, which is situated in the right ventricle. The change in blood temperature is measured at the distal port situated in the pulmonary artery and plotted over time, generating a thermal washout curve.[2]

Akin to both dye and lithium chloride dilution techniques, a modification of the Stewart-Hamilton equation is used to calculate CO if the volume of cold saline ($Vol_{injectate}$), temperature of the cold injectate ($T_{injectate}$), temperature of the blood (T_{blood}), average temperature measured by the thermistor (T_{mean}), and the times at which the temperature drop is first detected (T_1) and returns to normal (T_2), is known.[2]

$$CO = [Vol_{injectate} \times (T_{blood} - T_{injectate})] / [T_{mean} \times (T_2 - T_1)]$$

The temperature change is measured by two thermistors, one at the site of proximal injection and one downstream of the injection site. A thermistor is a temperature-sensitive resistor.[2] It is constructed from a semiconductor material with a resistance inversely proportional to temperature (negative temperature coefficient) and is known as a negative thermal conductivity thermistor.[2] They are small, cheap and exhibit excellent accuracy and rapid response times.[2] When connected to a Wheatstone bridge circuit, the resistance generated can be measured accurately. Furthermore, by passing a constant current (I) through the electrical circuit connected to the thermistor, a temperature change will result in a change in resistance (R) in the circuit, which in turn will result in a change in potential difference (V) across the circuit.[2] This change in potential difference allows electronic detection of the temperature change at the distal port on the PAFC.

The use of a PAFC can be avoided by the injection of cold injectate into a central venous catheter whilst measuring the resultant temperature change at a peripheral arterial line. This method is known as trans-pulmonary thermodilution and the resulting washout curve is less pronounced due to the circulation of injectate through both the right and left heart chambers as well as the pulmonary circulation before reaching the thermistor. The use of a PAFC to measure CO is still considered the gold standard, but its use has declined over the years. Whilst the PAC-Man study found no evidence of benefit or harm in its use in critically ill patients, its invasive nature, required technical skill and risk of complication have led to the use of less invasive CO monitors.[10]

Pressure waveform analysis and pulse pressure contour analysis

Pressure waveform analysis and pulse pressure contour analysis can be used to calculate CO from measurements obtained from a peripheral arterial catheter, based on theory first described by Erlanger and Hooker in 1904.[11] They theorised that CO was proportional to arterial pulse pressure.[12] Arterial pulse pressure is different from arterial blood flow. A German physiologist, Otto Frank, described the Windkessel phenomenon that explains the relationship between arterial pulse pressure and flow.[13] During systole, the contraction of the left ventricular musculature generates a pressure gradient between the left ventricle and the aorta. This pressure gradient (ΔP) drives the flow of blood (Q), which is proportional to the pressure exerted and the radius of the aorta (r) whilst being inversely proportional to the viscosity (η) of blood and the length (L) of the vasculature (Hagen-Poiseuille law).[14]

$$Q = (\Delta P \times \pi r^4) / (8 \times \eta \times L)$$

Some of the kinetic energy of the blood ejected into the aorta is converted into potential energy that is stored in the stretched elastic tissue of the vessel walls. During diastole, the aortic valve closes allowing the arterial pressure to fall, and the stored potential energy is converted back to kinetic energy during the elastic recoil of the vessel walls. This results in augmented diastolic blood flow and continual flow during diastole.

Pulse pressure contour analysis devices relate the shape of an arterial pressure wave to SV and systemic vascular resistance.[15] The steeper the upstroke of the arterial pressure waveform during systole, the greater the pressure and likely contractility, provided the aortic valve is not diseased.[15] The steeper the downstroke of the arterial waveform during diastole, the less elastic recoil and hence the lower the systemic vascular resistance.[15] The area under the pressure-time curve during the systolic part of the cardiac cycle is the mean arterial pressure during systole and is proportional to SV (Figure 2). While devices differ by making use of unique proprietary algorithms to calculate CO, they all aim to calculate SV.[15] SV is then multiplied by HR to determine CO.

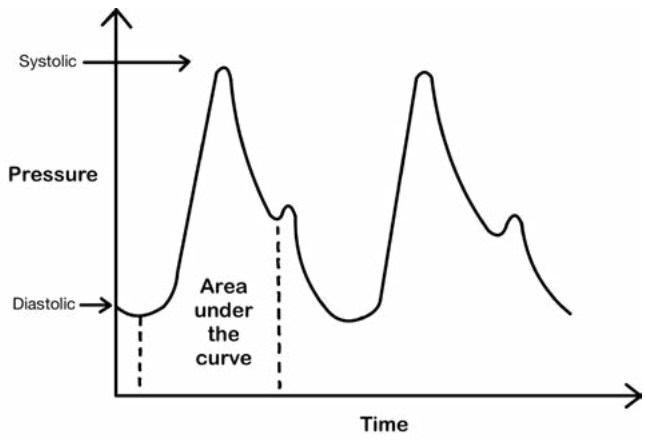

Figure 2: A graph depicting an arterial pulse pressure waveform

The use of arterial waveform analysis in the calculation of CO is made possible by signal transduction. A transducer is an electronic device that converts one form of energy to another.[2] In this instance, an arterial cannula is connected to a pressure transducer via a fluid-filled catheter. The fluid-filled catheter is pressurised, relatively inelastic and heparinised to ensure that it does not clot at the tip. This allows arterial pressure waves to be transmitted and reflected through the cannula to the transducer. The pressure transducer consists of four thin wafers of semiconductor material connected to form a Wheatstone bridge resistor network, bound to a membrane.[2] Small movements of the heparin-saline solution in the catheter are induced by the arterial pressure wave. This causes the pressure transducer diaphragm to oscillate. The oscillation causes a change in resistance and subsequent change in voltage generated across the Wheatstone bridge resistor network whilst a constant current is applied (Ohm's law).[2] This change in potential difference is displayed electronically as a change in gauge pressure relative to atmospheric pressure.[2] The pressure reading is continuously plotted against time to generate a pressure-time curve. An optimal arterial signal is required for the pulse pressure contour analysis calculation of CO.

Minimally invasive techniques

Ultrasound, aortic Doppler and echocardiography

Ultrasound and the Doppler principle can be used to calculate CO without the need for intravenous cannulation. This modality makes use of a lubricated ultrasound probe, placed either orally and advanced into the oesophagus in a minimally invasive approach, or suprasternal in a non-invasive approach.[7] The ultrasound probe contains a ceramic piezoelectric crystal that emits sound waves into the tissues at a frequency > 20 kHz when an alternating current is applied to it.[2] This causes the crystal to expand and contract repetitively, producing vibrations and emitting ultrasonic waves.[2] The high-frequency waves penetrate tissue while a variable number of waves are reflected at interfaces between tissues of differing densities.[2] Some waves travel further before being reflected and consequently return to the probe later. The kinetic energy of the reflected waves is converted back into an electrical signal when they return to the probe.[2] This electric signal is displayed on a monitor to provide a graphical representation of tissue at differing distances from the probe. If tissue is moving towards or away from the ultrasound probe, the reflected waves undergo a frequency shift before returning to the probe.[2] The change in frequency is termed the Doppler effect and can be used to calculate the velocity (Vel) of the moving tissue if the initial ultrasound frequency (F_o), Doppler shifted frequency (F_d), speed of ultrasound in tissue (C = 1 540 $m.s^{-1}$), and the angle of the ultrasound beam relative to the tissue (θ) is known, using the Doppler equation:[2]

$$Vel = (F_d \times C) / (2 \times F_o \times Cos\ \theta)$$

To calculate CO with the use of ultrasound, one must exploit its utility in measuring distances and velocities. The volume of a cylinder can be calculated if its length and cross-sectional area are known. Similarly, if the radius of the descending aorta is known (determined from nomograms based on the patient's height, weight and age, or by measurement on ultrasonography), and the velocity of red blood cells in the descending aorta is known (determined from the velocity-time integral = area under the velocity-time curve generated using the Doppler method above), one can calculate the volume of a cylinder of blood that moves through the aorta in one cardiac cycle (SV).[16] This, in turn, can be multiplied by HR to determine CO. Lastly, a correction factor needs to be applied to estimate the total CO since approximately 70% of the CO passes through the descending aorta.[16]

Non-invasive techniques

Bioimpedance

Thoracic electrical bioimpedance is one of the least invasive methods of calculating CO. This modality aims to estimate CO by exploiting Ohm's law. Ohm's law describes the relationship between potential difference (V), current flow (I), and resistance (R) in an electrical circuit as follows:[2]

$$V = I \times R$$

Impendence (Z) is the measure of resistance to electrical current when an alternating current is applied to the circuit.[7] Thus, bioimpedance is the measure of resistance offered by organic tissue to the conduction of an alternating current. Exploiting these principles enables the calculation of CO when a high frequency (alternating), low amplitude current is applied across the thorax. The thorax contains tissues with differing ionic concentrations and hence offers various impedances to current flow. Vascular-rich organs and blood vessels have high ionic content and are classified as low-impedance tissues (150 Ω/cm), whilst less vascular tissues are classified as high-impedance tissues (1 274 Ω/cm).[7] During systole, the aorta distends and the relative proportion of low-impedance tissue increases. By applying a constant alternating current to the thorax via electrodes placed on either side of the neck and the diaphragm, a change in impedance during the cardiac cycle can be inferred by a change in the potential difference between the electrodes.[7] SV is then calculated using the following formula:[12]

$$SV = VEPT \times VET \times EPCI$$

Where VEPT is the thoracic volume, VET is the ventricular ejection time determined from the R-R interval on the electrocardiogram, and EPCI is the ejection phase contractility index resulting from the product of bioimpedance and total fluid conductivity.[12] SV, in turn, is multiplied by HR to calculate CO.

Bioreactance

Bioreactance is an improvement on bioimpedance modalities because it reduces error due to movement artefacts, variance in patient body habitus, and inconsistencies in electrode positioning.[7] It relies solely on changes in phase shifts of alternating currents and voltages.[7]

Conclusion

Numerous CO modalities exist, each exploiting physical principles to aid the clinician in the perioperative management of patients. Their use as an adjunct to traditional clinical patient assessment may aid in the reduction of morbidity and mortality. At present, no ideal CO monitor exists, each has their strengths and limitations. An understanding of the physical principles will ensure appropriate interpretation of the data represented. This in turn will provide additional value in guiding appropriate therapeutic strategies.

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References

1. Dunn J-OC, Mythen MG, Grocott MP. Physiology of oxygen transport. BJA Educ. 2016;16(10):341-8. https://doi.org/10.1093/bjaed/mkw012.
2. Middleton B, Phillips J, Thomas R, Stacey S. Physics in anaesthesia. Oxfordshire: Scion Publishing, Ltd; 2012.
3. Kam P, Power I. Principles of physiology for the anaesthetist. 2nd ed. CRC Press; 2008.
4. Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. Chest. 2007;132(6):2020-9. https://doi.org/10.1378/chest.07-0073.
5. Lees N, Hamilton M, Rhodes A. Clinical review: goal-directed therapy in high risk surgical patients. Crit Care. 2009;13(5):231. https://doi.org/10.1186/cc8039.
6. Geerts BF, Aarts LP, Jansen JR. Methods in pharmacology: measurement of cardiac output. Br J Clin Pharmacol. 2011;71(3):316-30. https://doi.org/10.1111/j.1365-2125.2010.03798.x.
7. Betteridge N, Armstrong F. Cardiac output monitoring. Anaesth Intensive Care Med. 2022;23(2):101-10. https://doi.org/10.1016/j.mpaic.2021.10.018.
8. Fick A. On the measurement of blood mass in the heart ventricles. Sitzber Physik Med Ges Würzburg. 1870;36:16-28. German.
9. Fick A. V. on liquid diffusion. Lond Edinb Dublin Philos Mag J Sci. 1855;10(63):30-9. https://doi.org/10.1080/14786445508641925.
10. Harvey S, Harrison DA, Singer M, et al. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet. 2005;366(9484):472-7. https://doi.org/10.1016/S0140-6736(05)67061-4.
11. Erlanger J. An experimental study of blood-pressure and of pulse-pressure in man. Bull Johns Hopkins Hosp. 1904;12:145-378.
12. Funk DJ, Moretti EW, Gan TJ. Minimally invasive cardiac output monitoring in the perioperative setting. Anesth Analg. 2009;108(3):887-97. https://doi.org/10.1213/ane.0b013e31818ffd99.
13. Frank O. The basic shape of the arterial pulse. First treatise: mathematical analysis. J Mol Cell Cardiol. 1990;22(3):255-77. https://doi.org/10.1016/0022-2828(90)91460-O.
14. Pfitzner J. Poiseuille and his law. Anaesthesia. 1976;31(2):273-5. https://doi.org/10.1111/j.1365-2044.1976.tb11804.x.
15. Saugel B, Kouz K, Scheeren TWL, et al. Cardiac output estimation using pulse wave analysis-physiology, algorithms, and technologies: a narrative review. Br J Anaesth. 2021;126(1):67-76. https://doi.org/10.1016/j.bja.2020.09.049.
16. Drummond KE, Murphy E. Minimally invasive cardiac output monitors. BJA Educ. 2011;12(1):5-10. https://doi.org/10.1093/bjaceaccp/mkr044.

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FCA REFRESHER COURSE

Direct oral anticoagulants

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Keywords: direct oral anticoagulants, prophylactic anticoagulation indications, therapeutic anticoagulation indications

Introduction

Direct oral anticoagulants (DOACs) have become the standard of care for a wide range of prophylactic and therapeutic anticoagulation indications. They offer major advantages:

1. Compared with heparin, low molecular weight heparins (LMWH), and pentasaccharides, DOACs have an enteral route (increased suitability for long-term use) and increased predictability of response across a range of patient pathophysiological states.
2. Compared with oral vitamin K antagonists (e.g. warfarin) DOACs have a more rapid onset and offset of action (allowing early surgery after discontinuation), a predictable dose-response relationship obviating the need for monitoring, a wider therapeutic window, reduced bleeding risk (especially intracerebral), and relatively few food and drug interactions.

DOACs bind directly to the active site of their enzyme target and inhibit its further participation in the coagulation cascade. Both free and clot-bound thrombin and/or factor Xa are targeted. They are comprised of drugs from two pharmacological categories:

1. Direct thrombin (factor II) inhibitors (unlike heparins, LMWH, and pentasaccharides that inhibit factor II via an amplification process involving antithrombin). In South Africa, the sole available agent from this category is dabigatran etexilate.
2. Factor Xa inhibitors. This group is represented by rivaroxaban and apixaban. The release of edoxaban and betrixaban is anticipated.

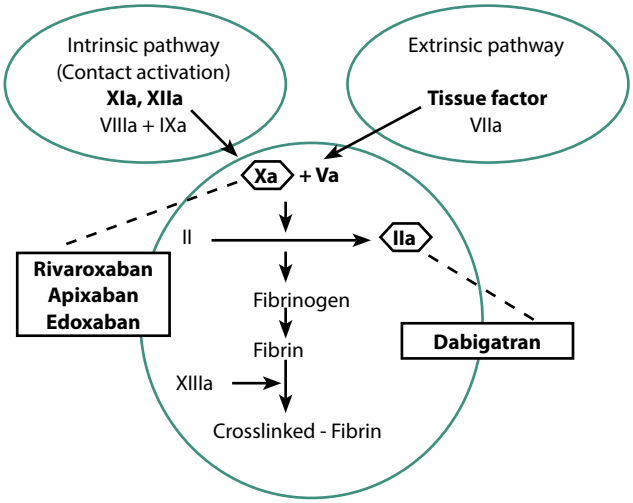

Figure 1: Schematic view of location of action of DOACs[1]

Therapeutic indications

Table I: DOACs on-label therapeutic indications

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Stroke prevention in AF – non-valvular	Yes – intermediate-risk cases	Yes – including high-risk patients	Yes	Yes
DVT prophylaxis in major surgery/major medical disease	Yes – ortho	Yes – ortho/malignancy surgery	Yes – ortho	No
Long-term prophylaxis after recurrent VTE/ thrombophilia/malignancy	Yes Not for malignancy	Yes	Yes	No
Treatment of acute VTE	Yes – after the initial LMWH treatment	Yes	Yes	Yes
Prophylaxis with mechanical heart valves	Only bioprosthetic valves	Only bioprosthetic valves	Only bioprosthetic valves	Only bioprosthetic valves
Anticoagulation with ACS/coronary stents/ chronic CAD (part of DAPT with aspirin or P2Y12 inhibitor)/PVD	No	Yes	No	No

Notes on Table I:
- The on-label indications are expanding as phase 3 trials are concluded for the newer agents. All factor Xa antagonists will likely, in time, share the indications that apply to rivaroxaban. You will already encounter agents used off-label for the full spectrum of indications. DOACs were used extensively during the COVID-19 pandemic.
- In general, prophylactic doses are 50–66% of therapeutic doses and are applied after major surgery and to medically ill inpatients.
- Prophylaxis in stroke prevention in atrial fibrillation (SPAF) and cardiac bioprosthetic valves is at 66–100% of treatment doses.
- Rivaroxaban doses for coronary artery disease are half of prophylactic doses, provided it is used in combination with an anti-platelet agent.
- Dabigatran and (less so) apixaban require downward dose adjustment in the presence of renal dysfunction and dabigatran should not be used in patients with creatinine clearance < 30 ml/min.

Pharmacokinetics

Table II: Pharmacokinetics (PK) of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Doses	SPAF 220–300 mg/day Prophylaxis 150–220 mg/day VTE treatment 300 mg/day	SPAF 20 mg daily Prophylaxis 10 mg/day VTE treatment 15 mg *bid* followed by 20 mg daily after 21 days	SPAF 5 mg *bid* Prophylaxis 2.5 mg *bid* VTE treatment 10 mg *bid* for 7 days then 5 mg *bid*	SPAF 60 mg daily Treatment of VTE 60 mg daily
T_{max}	1.5 hours	2–4	1–4	1–2
$T_{1/2}$	9–17 hours (average 12)	5–13 (average 9)	12	10–14
Elimination	80–85% renal	33% renal	25–27% renal	35–50% renal
Other PK features	Absorption inhibited by PPI Prodrug	Safe in mild liver disease	Reduced dose in mild liver disease; mass < 60 kg and age > 80 years	Safe in mild liver disease
Dose adjustment	Halve dose if creatinine clearance < 50 ml/min. Contra-indicated < 30	Halve dose at creatinine clearance < 30 ml/min; contra-indicated in ESRD	Same as for rivaroxaban	Same as for rivaroxaban

Notes on Table II:
- All agents are subject to increased metabolism and decreased efficacy from P-glycoprotein inducers (e.g. rifampicin) and increased efficacy from P-glycoprotein inhibitors (e.g. ketoconazole).
- All Xa inhibitors show similar changes with CYP3A4 inducers (e.g. carbamazepine and phenytoin) and inhibitors (e.g. HIV protease inhibitors). Antiarrhythmics may also interact to reduce metabolism and increase bleeding risk.
- Increasing drug doses increases antithrombotic efficacy but at the expense of an increased risk of bleeding. Bleeding risk is, in general, lower than that of warfarin at equi-effective doses (< 2% per annum risk of major bleeding).

Contraindications

1. Conditions with a high bleeding risk (e.g. gastrointestinal [GI], varices, recent/acute intracerebral bleeding, or major neuro or ophthalmic surgery).
2. Concurrent use of other anticoagulants; however, may be used concurrently with anti-platelet drugs.
3. Severe or end-stage liver or kidney disease. Dabigatran is specifically contraindicated in kidney disease with functional impairment that is moderate or worse (glomerular filtration rate < 50 ml/min). All other DOACs require dose reduction in moderate kidney impairment and only rivaroxaban can be used with severe impairment (creatinine clearance 15–30 ml/min with a 50% dose reduction).
4. Old age and body mass < 60 kg also mandate a dose reduction.

Bleeding

As stated previously, major bleeding rates are lower than those of warfarin and comparable to LMWH (< 2% per annum). Bleeding is frequently lower GI in nature and at surgical sites (at a similar rate to warfarin). Intracerebral bleeding is less frequent than with warfarin because DOACs do not inhibit factor VII, which is the dominant mediator of haemostasis in the cerebral circulation.

Because of the relatively short half-lives of DOACs, time and supportive measures (including infusion of clotting factors and prothrombin complex concentrate) are usually sufficient to deal with major drug-related coagulopathic bleeding, which should settle within 12–24 hours except in the presence of renal dysfunction. The four-factor prothrombin complex concentrates (PCC) are substantially more effective than FFP if urgent restoration of haemostasis is required. Should surgical urgency not permit a delay until drug activity has diminished, these agents should be available in theatre for early use if coagulopathic bleeding starts. Prophylactic use of PCC or specific reversal modalities should only be considered for procedures with prohibitive bleeding risk (e.g. neurosurgery in patients at high risk of bleeding or renal dysfunction and with clinical and laboratory evidence of critically high levels of anticoagulant). PCC, at doses > 25 IU/kg achieve a 66% moderate-to-good response rate in bleeding patients on Xa inhibitors; largely due to factor II in PCC bypassing the drug target site. The response rate with dabigatran is poorer since the target site of the drug is thrombin itself. Specific reversal (discussed below) is therefore recommended as a first-line intervention for severe dabigatran-related bleeding. The role of fibrinogen concentrates in the cessation of bleeding from all DOACs is still under investigation.

Antidotes for uncontrollable DOAC-related bleeding

Early oral activated charcoal and haemodialysis may be of use in known cases of recent dabigatran ingestion. Specific antidotes have now been registered for the rare instance of otherwise uncontrollable DOAC-related bleeding:

1. Idarucizumab (Praxbind) for dabigatran is available in South Africa. This is a humanised monoclonal antibody fragment that binds and removes dabigatran from its site of action, eliminating its plasma presence within minutes and its anticoagulant effect within 2.5 hours. A dose of 5 g intravenous over 5–10 minutes will abort the majority of dabigatran-related bleeds. A repeat dose may be given if needed. It has no

intrinsic prothrombotic effect. This treatment is very costly at around R50 000 per treatment course.

2. Andexanet alfa (Ondexxya) is an inactive recombinant factor Xa analogue that acts as a surrogate target and binds and sequesters Xa antagonists (proven effect for rivaroxaban and apixaban thus far), rapidly reducing their activity in healthy volunteers. Trials in patient populations suggest an 89% successful reversal rate. Bolus doses of 400–800 mg are given at 30 mg/min, followed by ongoing infusions of 400–800 mg over the next two hours. Hypersensitivity-type infusion reactions are common. There is a prothrombotic signal in 30 days after its use. The cost per utilisation is that of a new, medium size car. This agent is still unavailable in South Africa.
3. Ciraparantag is a small synthetic cationic molecule, shown to bind to and reverse the effect of heparins and DOACs. It remains in phase 2 trials.

Irrespective of the management strategy employed to prevent or control bleeding, it is essential to understand that the initial indication for a DOAC persists and that anticoagulation must be resumed at the earliest opportunity to curtail intrinsic and reversal-related prothrombotic influences. In the non-emergent surgical setting, drug discontinuation for three half-lives should ensure that the drug effect is inconsequential. It is important to factor in patient risk factors, particularly renal function when making this calculation.

Monitoring of DOACs

Table III: Available laboratory assays for DOACs

	Dabigatran	Anti-Xa
INR	No	Suggestive but may yield false negatives with rivaroxaban More predictable concentration-response derangement with other Xa antagonists
aPTT	Suggestive at peak drug levels, aPTT prolonged 1.5–1.8 times	Weakly suggestive
Thrombin time	Sensitive concentration-response relationship	Relatively to entirely insensitive
Ecarin clotting time	Sensitive	No
Specific anti-Xa assay	No	Available internationally Quantitative
Fibrinogen	Levels affected but not quantitative	No

Notes on Table III:

- Other than specific anti-Xa analysis, tests are relatively unpredictable in terms of the drug concentrations but helpful in identifying the drug group.
- A combination of tests yields greater accuracy.
- Viscoelastic tests may indicate the extent of coagulopathy in severe intoxication but will not identify the drug responsible. Since they are provoked tests, they may underestimate the extent of the coagulopathy. Despite this, the tests may reveal other coagulation abnormalities (e.g. fibrinolysis, which can be used to guide the administration of specific procoagulants, such as tranexamic acid).

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References

1. Intagliata NM, Maitland H, Caldwell SH. Direct oral anticoagulants in cirrhosis. Curr Treat Options Gastroenterol. 2016;14(2):247-56. https://doi.org/10.1007/s11938-016-0092-0.
2. Joubert I, Beeton A. Chapter 21. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed.
3. Hurst K, Lee R, Handa A. Quick reference guide to the new oral anticoagulants. J Vasc Surg. 2016;63(6):1653-7. https://doi.org/10.1016/j.jvs.2016.02.054.
4. Laslo CL, Bacalbasa N, Stanescu AMA, et al. New oral anticoagulants - possible extension to other indications (review). Exp Ther Med. 2020;20(3):2401-5. https://doi.org/10.3892/etm.2020.8713.
5. Spahn DR, Beer J-H, Borgeat A, et al. NOACs in anesthesiology. Transfus Med Hemother. 2019;46(4):282-93. https://doi.org/10.1159/000491400.
6. Dubois V, Dincq A-S, Douxfils J, et al. Perioperative management of patients on direct oral anticoagulants. Thromb J. 2017;15(14). https://doi.org/10.1186/s12959-017-0137-1.
7. Shah SB, Pahade A, Chawla R. Novel reversal agents and laboratory evaluation for direct-acting oral anticoagulants (DOAC): an update. Indian J Anaesth. 2019;63(3):169-81. https://doi.org/10.4103/ija.IJA_734_18
8. Chen A, Stecker E, Warden BA. Direct oral anticoagulant use: a practical guide to common clinical challenges. J Am Heart Assoc. 2020;9(13):e017559. https://doi.org/10.1161/JAHA.120.017559.
9. Grottke O, Schulman S. Four-factor prothrombin concentrate for the management of patients receiving direct oral activated factor X inhibitors. Anesthesiology. 2019;131(5):1153-65. https://doi.org/10.1097/ALN.0000000000002910.
10. Cuker A, Burnett A, Triller D, et al. Reversal of direct oral anticoagulants: guidance from the anticoagulation forum. Am J Hematol. 2019;94(6):697-709. https://doi.org/10.1002/ajh.25475.
11. Eikelboom JW, Kozek-Langenecker S, Exadaktylos A, et al. Emergency care of patients receiving non-vitamin K antagonist oral anticoagulants. Br J Anaesth. 2018;120(4):645-56. https://doi.org/10.1016/j.bja.2017.11.082.
12. Kim K-S, Song JW, Soh S, Kwak Y-L, Shim J-K. Perioperative management of patients receiving non-vitamin K antagonist oral anticoagulants: up-to-date recommendations. Anesth Pain Med (Seoul). 2020;15(2):133-42. https://doi.org/10.17085/apm.2020.15.2.133.

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FCA REFRESHER COURSE

Cerebral physiology

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Keywords: cerebral physiology, perfusion, oxygen delivery

Introduction

The brain is a very interesting and complex organ. To sustain consciousness, satisfactory perfusion and adequate oxygen delivery are vital.[1] As the brain has relatively little capacity for energy storage, a continuous supply of oxygen and nutrients must be delivered by uninterrupted cerebral blood flow (CBF).[2]

Cerebral metabolic rate (CMR)

The brain has the highest metabolic requirements of any organ in the body, as reflected by its high blood flow rate.[3] The CMR is the rate at which the brain utilises metabolic substrates, e.g. oxygen ($CMRO_2$), glucose (CMRglu), or generates by-products, e.g. lactate (CMRlact).[4] The brain's oxygen consumption accounts for 20% of basal oxygen consumption (50 ml min^{-1}) at rest and relies almost completely on the oxygen-dependent metabolism of glucose for energy production. Because CBF is adjusted to meet the metabolic demand, oxygen in the grey matter is approximately five times more than in the white matter. Normal values for CBF, CMR, and other physiological variables are provided in Table I.

Table I: Cortical (mostly grey matter), sub-cortical (mostly white matter), and other physiological values[5]

Normal cerebral physiological values	
Global	44–55 ml/100 g/min
Cortical	75–80 ml/100 g/min
Sub-cortical	20 ml/100 g/min
CMR of oxygen	3–3.5 ml/100 g/min
Cerebral vascular resistance (CVR)	1.5–2.1 ml/100 g/min
Cerebral venous oxygen	3 244 mmHg
Cerebral venous oxygen saturation	55–70%
Intracranial pressure (ICP)	8–12 mmHg

Glucose is not only the main energy substrate for the brain, but also a precursor for neurotransmitters, including gamma-aminobutyric acid (GABA), glutamate, and acetylcholine, and is essential to maintain a constant CBF and therefore the substrate supply.[6] Under aerobic conditions, oxidative phosphorylation produces 38 molecules of adenosine triphosphate (ATP) for every molecule of glucose. Of the energy produced, 60% is utilised for the electrophysiological functioning of the neurons (i.e. their chemical and electrical activity). The other 40% is to maintain the integrity and homeostasis of the neuronal cells.[3,7]

The brain has a limited capacity for anaerobic metabolism, and under these conditions, one molecule of glucose undergoes glycolysis to produce only two molecules of ATP. The lactate produced anaerobically is utilised to carry out the fundamental processes essential to maintain the cell structure. Aerobic metabolism is restored if perfusion is re-established immediately, otherwise, permanent cell death follows.[8]

The CMR decreases during sleep and increases during sensory stimulation, mental tasks, or arousal of any kind. During epileptic activity, increases in the CMR may be extreme, whereas regionally, after brain injury and globally with coma, the CMR may be substantially reduced. In general, anaesthetic drugs suppress the CMR, apart from ketamine and nitrous oxide (N_2O). The electrophysiological function is the component on which the CMR acts.

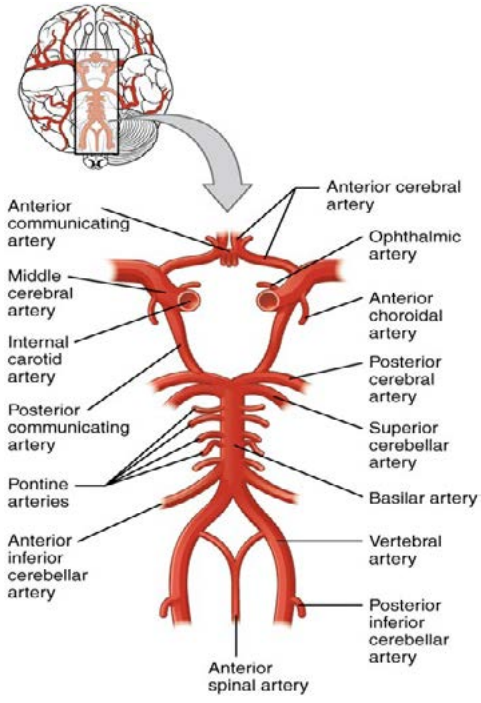


Figure 1: The cerebral arterial system[10]

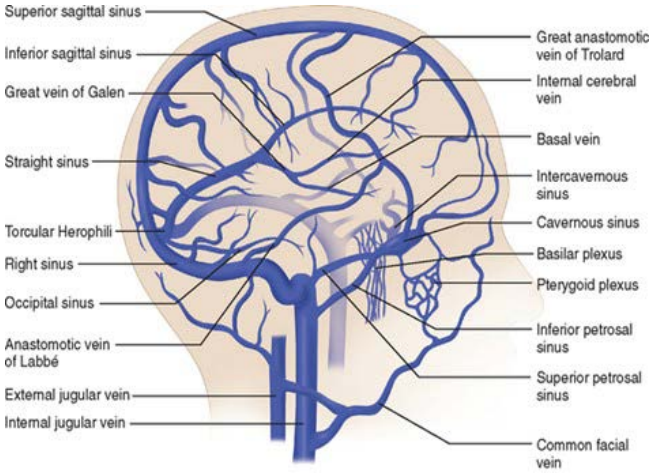


Figure 2: The brain venous system[11]

The cerebral circulation

The arterial blood supply to the brain is composed of paired right and left internal carotid arteries, which give rise to the anterior circulation, and paired right and left vertebral arteries, which give rise to the posterior circulation. The connection of the two vertebral arteries forms the basilar artery. The internal carotid arteries and the basilar artery connect to form a vascular loop, called the circle of Willis, at the base of the brain. This permits collateral circulation between both the right and left and the anterior and posterior perfusing arteries. Three paired arteries that originate from the circle of Willis perfuse the brain, i.e. anterior, middle, and posterior cerebral arteries. The posterior communicating arteries and the anterior communicating artery complete the loop. The anterior and the posterior circulations contribute equally to the circle of Willis (Figure 1) .[3,9]

Three sets of veins drain blood from the brain. The superficial cortical veins are within the pia mater on the brain's surface. Deep cortical veins drain the deeper structures of the brain. These veins drain into dural sinuses, of which the superior and inferior sagittal sinuses and the straight, transverse, and sigmoid sinuses are the major dural sinuses. These ultimately drain into the right and left internal jugular veins (Figure 2).[3]

Cerebral blood flow (CBF)

The adult human brain weighs approximately 1 350 g and therefore represents approximately 2% of total body weight; however, it receives 12–15% of cardiac output. The CBF is best described by the Hagen-Poiseuille equation for laminar flow, which demonstrates a direct relationship between flow, cerebral perfusion pressure (CPP), and the calibre of cerebral vessels:

$$CBF = \frac{\pi \Delta P r^4}{8 \mu l}$$

Where π is the mathematical constant, ΔP is the pressure gradient (which is the CPP), r is the radius/calibre of the blood vessel, μ is the dynamic viscosity of blood, and l is the length of the blood vessel. CBF will thus improve if the CPP increases, and the cerebral vasculature is vasodilated.[1]

Under conditions of normothermia and normoxia, CBF must remain at 50–60 ml/100 g/min to meet the metabolic demands of the functioning brain.[2,12] Loss of consciousness ensues within seconds of ischaemia secondary to a reduction in CBF, with permanent brain damage occurring within 3–8 minutes of insufficient blood supply.[6,8] Reserve blood flow exists to a point, but ischemic injury generally occurs once CBF drops below 22 ml/100 g/min, although concurrent pathologies such as traumatic brain injury (TBI) or hypothermia can change this threshold.

Indirect measures are often used to estimate the adequacy of CBF and brain tissue oxygen delivery in clinical settings. These methods include transcranial Doppler, near-infrared spectrometry, brain tissue oximetry, and intracerebral microdialysis.[6]

Perfusion pressure: CPP is the difference between the mean arterial pressure (MAP) and the ICP or central venous pressure (CVP) if it is greater than ICP. Because ICP is not usually measured in normal subjects, changes in MAP will thus largely govern the perfusion pressure and hence CPP is primarily dependent on MAP.[6]

CPP = MAP - ICP (or CVP)

Patients with CPP < 50 mmHg show slowing on the electroencephalogram (EEG), and those < 25 mmHg typically have a flat EEG.[3,6] The regulatory mechanisms that preserve CBF can broadly be categorised into cerebral autoregulation (CA), neurovascular coupling (NVC), and vasomotor reactivity (VMR).

Cerebral autoregulation (CA)

Autoregulation of blood flow exists to ensure that perfusion of vital organs remains intact and stable across the dynamic range of pressures to which the vascular bed is exposed. CA can broadly be defined as a proportional change in CVR in response to changes in perfusion pressure to maintain a constant blood flow.[2]

$$CBF = \frac{CPP}{CVR}$$

Autoregulation is believed to occur via a myogenic mechanism whereby an increase in MAP increases the transmural vessel tension causing depolarisation of vascular smooth muscle and constriction of the precapillary resistance vessels. The reverse happens when the MAP and transmural tension decrease.[1] The range of MAP the CA mechanism can respond to was first described in humans by Lassen in 1959. From this work, the autoregulation curve was generated, which depicts a plateau region wherein CBF is stable across a MAP range of 50–150 mmHg. It is an almost instant process that occurs within 1–10 seconds of a change in pressure (Figure 3).[2]

Below the lower limit of autoregulation, approximately 50 mmHg in humans, and above the upper limit, approximately 150 mmHg, the cerebral circulation is pressure passive and CBF decreases or increases, respectively, with corresponding changes in MAP. In chronic arterial hypertension, the upper

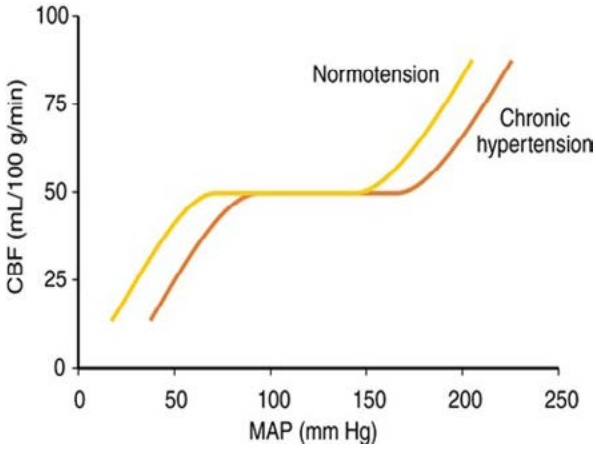


Figure 3: Autoregulation curve[13]

and lower limits of autoregulation are both displaced to higher levels, shifting the curve to the right (Figure 3), and cerebral hypoperfusion occurs at higher values of MAP compared with healthy individuals. Flow becomes more pressure-dependent at low "normal" arterial pressures in return for cerebral protection at higher arterial pressures.[1,6] Cerebral vasculature is known to be highly innervated by the autonomic nervous system (ANS), and postsynaptic adrenergic receptors are present on vascular smooth muscle. Denervation does not alter resting CBF and only modestly reduces the upper limit of the autoregulatory curve.[2]

The vascular smooth muscle, endothelium, and neighbouring neurons and astrocytes, collectively referred to as the neurovascular unit, play direct and modulatory roles in establishing myogenic tone. Mechano-sensitive transient receptor potential (TRP) channel family members, present throughout the cerebral vasculature, have recently been identified as a component of the pressure detection mechanism of the neurovascular unit. These channels respond to stretch and/or shear forces, resulting in cation conductance ultimately leading to vasoconstriction.[2]

The density of innervation declines with vessel size, and the greatest neurogenic influence appears to be exerted on larger cerebral arteries. This innervation includes cholinergic (parasympathetic and non-parasympathetic), adrenergic (sympathetic and non-sympathetic), serotoninergic, and VIPergic systems of extra-axial and intra-axial origin.

Factors affecting autoregulation include arterial carbon dioxide tension ($PaCO_2$), arterial oxygen tension (PaO_2), neurogenic control, temperature, and rheology.

Neurovascular coupling (NVC)

Increased neuronal activity results in increased local brain metabolism. This increase in the CMR is associated with a proportional change in CBF referred to as NVC. It is a positive feedback mechanism wherein increased neuronal activity results in energy demand; this demand is met by an increase in CBF.[3] This process occurs at the level of the cerebral microvasculature of pial arterioles outside the pia mater and penetrating parenchymal arterioles (Figure 5, pink inlay). The mechanism by which the tone of these vessels is matched to the needs of the surrounding neurons is complex and involves all members of the neurovascular unit.

In response to excitatory glutamatergic inputs, active neurons release nitric oxide that diffuses to nearby vascular smooth muscle and promotes dilation. Adenosine produced from the extracellular conversion of neuron- and astrocyte-derived ATP diffuses to vascular smooth muscle and induces changes in vascular tone. Neuron-derived prostaglandins also influence vascular tone. Prostaglandin E2 is produced by active pyramidal neurons and acts on EP2 and EP4 receptors present in cerebral vascular smooth muscle resulting in vasodilation.

Additionally, GABAergic interneurons release numerous vasoactive mediators directly onto vascular smooth muscle.[2] Metabolically active astrocytes that envelope the parenchymal arterioles also mediate the tone of the vascular smooth muscle. Glia also plays an important role in NVC. Their processes contact neurons, and these processes may serve as conduits for the coupling of increased neuronal activity to increases in blood flow.[3] Finally, in response to neuronal activity, the endothelium itself propagates vasodilatory signals throughout the vasculature of active cortical regions. Collectively, these mechanisms allow for the modulation of CBF that is temporally and spatially correlated with neuronal activity.

Vasomotor reactivity (VMR)

PCO_2

The cerebral vasculature tone is influenced by changes in arterial blood CO_2 and, to a lesser extent, O_2 tension through a process referred to here as VMR (Figure 5, green inlay). VMR to CO_2 is stronger in the brain compared to other organs. Both pial arterioles and large calibre cerebral vessels respond. Alteration of cerebral vascular tone in response to changes in $PaCO_2$ is an intrinsic property of the vasculature and occurs independent of adrenergic activity, despite extensive innervation by the sympathetic nervous system. This mechanism establishes a roughly linear relationship between CBF and acute $PaCO_2$ changes, with a 1–2 ml/100 g/min for each 1 mmHg change in $PaCO_2$ across a range of 20–80 mmHg (Figure 4).[6] Adaptation to chronic alteration of $PaCO_2$ occurs and CBF will tend to normalise over a 6–8 hour period.[2,6] This response is attenuated at a $PaCO_2$ less than 25 mmHg (Figure 4, blue).

The magnitude of the reduction in CBF caused by hypocapnia is more intense when resting CBF is increased (as might occur during anaesthesia with volatile agents). Conversely, when resting CBF is reduced, the magnitude of the hypocapnia-induced reduction in CBF is decreased slightly. Accordingly, anaesthetic drugs that alter resting CBF cause changes in the response of the cerebral circulation to CO_2. The level of $PaCO_2$ also modulates CA. With hypercarbia, CA response to hypertension is attenuated. In contrast, with the induction of hypocapnia, CBF is autoregulated over a wider MAP range.[3]

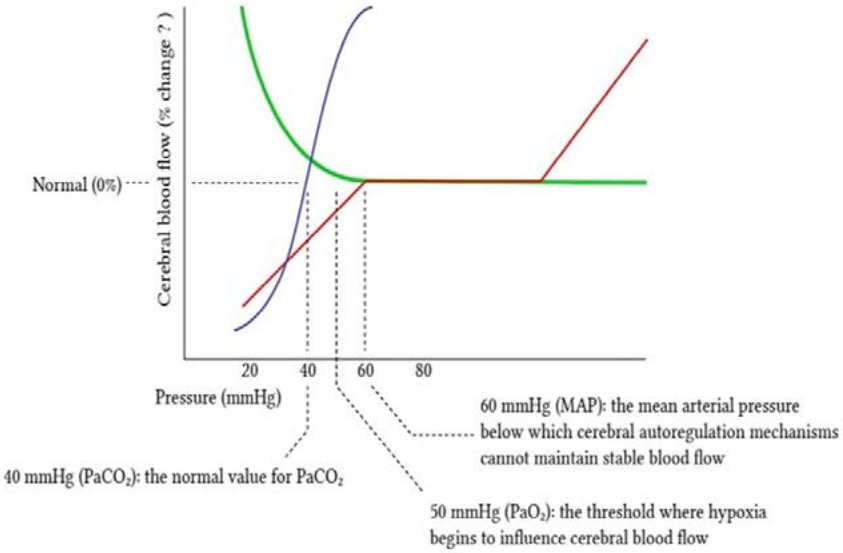
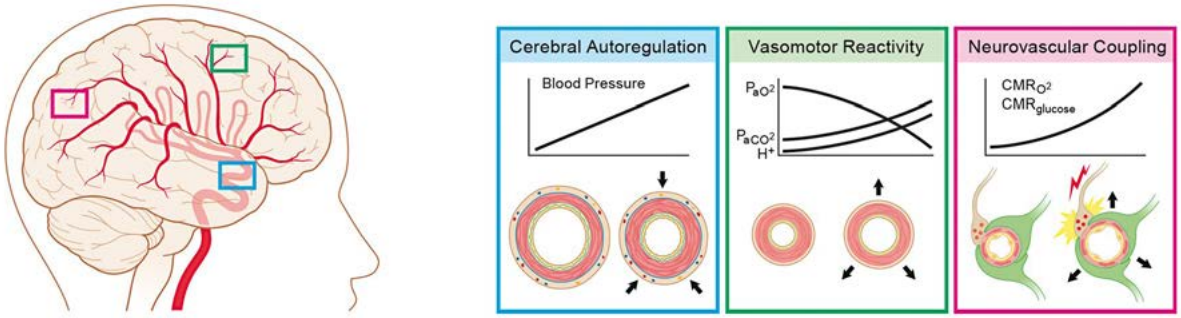


Figure 4: Factors affecting CBF, PaO_2, and $PaCO_2$[14]

PaO_2

Changes in PaO_2 from 60 to more than 300 mmHg have little influence on CBF. A reduction in PaO_2 below 60 mmHg rapidly increases CBF. Below a PaO_2 of 60 mmHg, there is a rapid reduction in oxyhaemoglobin saturation (Figure 4). Below this level, oxygen-sensitive ion channels in the smooth vascular muscles are activated and vasoactive substances, such as nitric oxide, adenosine, prostacyclin, angiotensin, vasopressin, and opioids, are released. An imbalance in these mediators is responsible for the vasodilatation and increases in CBF during hypoxaemia.[1]

The relationship between oxyhaemoglobin saturation, as evaluated by pulse oximetry, and CBF is inversely linear.[3] Vasodilation occurs independent of peripheral chemoreceptors and may be accompanied by a small increase in the CMR of oxygen ($CMRO_2$). Under hypoxic conditions, the hypocapnic cerebral vasoconstriction activity is attenuated. This prevents ischemic injury from arising due to hyperventilation-induced hypocapnia associated with hypoxic ventilatory drive.[2] Increasing oxygen will have the opposite effect and cause vasoconstriction, which is not clinically significant.



GOM	CBF		CA	VMR	NVC
CMRO2 reduced	Increased	*Volatile Anesthetics*	> 1.5 MAC (Isoflurane, Desfluare) > 1 MAC sevoflurane	> 1.5 MAC (Isoflurane, Desfluare) > 1 MAC sevoflurane	Unknown
	Increased	*Nitrous Oxide*			Unknown
CMRO2 reduced	Region specific reduction	*Xenon*			Unknown
CMRO2 reduced	Reduced	*Propofol*	> 200 mcg/kg/min	Mixed Results	Unknown
CMRO2 increased	Increased	*Ketamine*			Unknown
CMRO2 reduced	Reduced	*Etomidate*			Unknown
CMRO2 reduced	Reduced	*Dexmedetomidine*			Unknown
	Dose and agent specific biphasic responses	*Opioids*			Unknown
CMRO2 reduced	Reduced	*Benzodiazepines*			Unknown
CMRO2 reduced	Reduced	*Barbiturates*			Unknown
	Dose and agent specific biphasic responses	*Lidocaine*			Unknown
		Regional Anesthesia	Stellate Ganglion Block		Unknown

Figure 5: Summary of the effects of anaesthetic agents on global oxidative metabolism (GOM) and CBF, as well as the endogenous regulatory mechanisms such as CA, VMR, and NVC[2,15]

Temperature

Decreasing temperature decreases cerebral metabolism, and the reverse occurs when temperature is increased. For every 1 °C decrease in brain temperature, the CMR and hence the CBF decrease by 7%.[6] CBF is nearly halved at a temperature of 27 °C and the $CMRO_2$ is as low as 10% of normal at 18 °C, allowing preservation of brain function during episodes of deep hypothermic circulatory arrest. Mild hypothermia causes vasoconstriction, which decreases CBF and ICP but has failed to improve outcomes in patients with traumatic head injury.

Cooling to 32–34 °C is recommended in postcardiac arrest patients and as a treatment of raised ICP refractory above other treatment modalities.[1] Hypothermia decreases the rate of energy utilisation associated with both the electrophysiological function and the basal component related to the maintenance of cellular integrity. Mild hypothermia preferentially suppresses the basal component of the CMR.[3]

Hyperthermia has the opposite influence on cerebral physiological function. Between 37 °C and 42 °C, CBF and CMR increase, after which protein degradation occurs with a resultant decrease in $CMRO_2$. However, above 42 °C, a dramatic reduction in cerebral oxygen consumption occurs, an indication of a threshold for a toxic effect of hyperthermia that may occur because of protein (enzyme) denaturation.

Rheology

Blood viscosity can influence CBF. Hematocrit is the single most important determinant of blood viscosity. In healthy humans, variation of the haematocrit within the normal range (33–45%) probably results in only modest alterations in CBF. Beyond this range, changes are more substantial. In anaemia, CVR is reduced and CBF increases. However, this may result not only from a reduction in viscosity but also as a compensatory response to reduced oxygen delivery.[3] Under ischaemic conditions, low CPP causes a low flow state resulting in compensatory vasodilation and, during these circumstances, decreasing the viscosity of blood may improve CBF. Despite this, a reduction in haematocrit also lowers the oxygen content of blood, which may exacerbate an ischaemic insult.[1]

Intracranial pressure (ICP)

The intracranial contents consist of 80% brain volume, 10% cerebrospinal fluid (CSF), and 10% blood. The concept of ICP can best be understood if we compare the brain to a closed box or a fixed and rigid structure. The Monro-Kellie hypothesis states that the volume of the brain and its constituents inside the bony cranium is fixed and cannot be compressed. Any increase in one component must be offset by an equivalent decrease in another to prevent a rise in ICP.[1,9]

In adults, ICP is normally 8–12 mmHg when supine and is posture-dependent, being lowest in the upright position. There is an initial compensation that prevents major changes in intracranial compliance with minimal increases in ICP. A critical point is reached when further volume increases produce precipitous rises in ICP, with a reduction in CPP and cause cerebral ischaemia (Figure 6), ultimately causing local compression and herniation of brain tissue against the:

- cingulate gyrus under the falx cerebri;
- the uncinate gyrus through the tentorium cerebelli;
- cerebellar tonsil through the foramen magnum; or
- transcalvarial.[3,6]

Blood and CSF provide the main protection to the brain when the intracranial volume increases. Blood, has the most significant role in compensation for ICP changes as the cerebral venous volume can be changed promptly and hence ICP can be modified almost immediately. CSF plays an important role in compensating for increases in ICP by spatial compensation, whereby an increase in the volume of an intracranial constituent will cause a decrease in intracranial CSF volume by displacing CSF into the spinal canal.

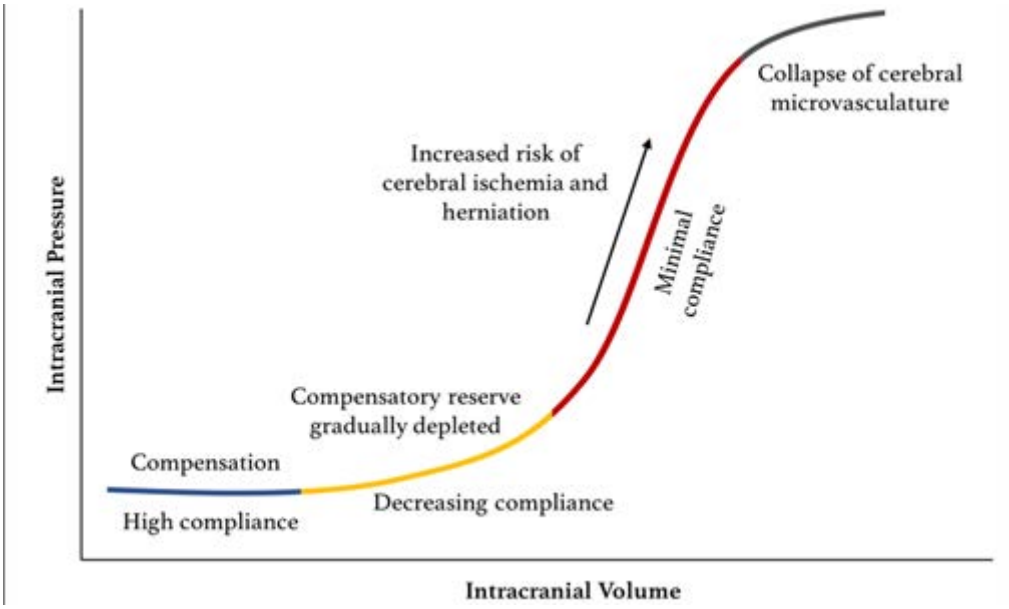


Figure 6: Pressure volume curve for ICP[16]

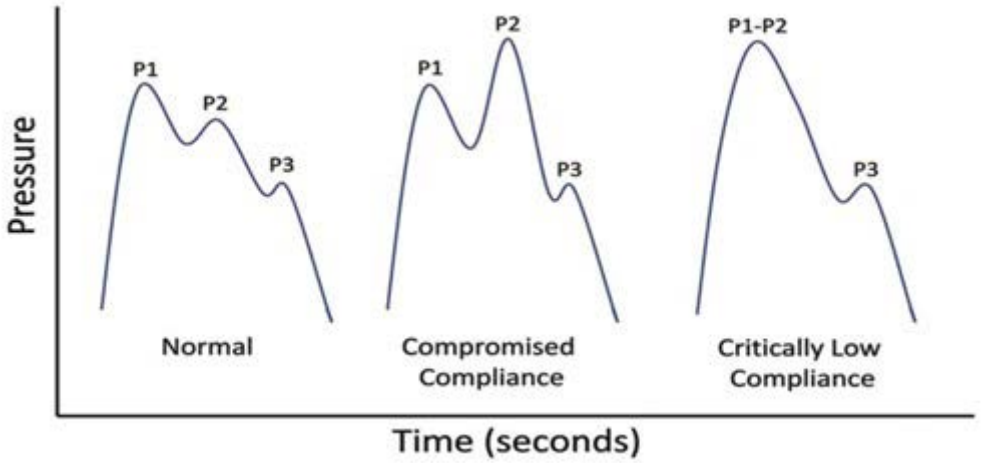


Figure 7: Intracranial waveforms[17]
P1 – pulsation of arterial vessels, percussion wave; P2 – brain compliance, tidal wave; P3 – closure of aortic valve, dicrotic wave

Spatial compensation occurs slowly and is significant in tumours that expand gradually but provides limited compensation for acute and sudden increases in ICP.[2] Major compensatory mechanisms include:

- an initial displacement of CSF from the cranial to the spinal compartment;
- an increase in CSF absorption;
- a decrease in CSF production; and
- a decrease in total cerebral blood volume (CBV, primarily venous).[6]

Intracranial elastance is determined by measuring the change in ICP in response to a change in intracranial volume. Figure 7 depicts ICP waveforms with compromised brain compliance. Normal waveform shows P1 exceeds P2, which exceeds P3. With compromised intracranial compliance P2 exceeds P1. With critically low compliance, P1 and P2 merge.

Cerebrospinal fluid (CSF) formation and circulation

CSF is the fluid present extracellularly between the arachnoid and pia mater and in the ventricles, providing buoyancy to the brain. It is produced mainly by the choroid plexus in the lateral, third, and fourth ventricles at a rate of 0.3–0.4 ml/min^{-1} (500 ml day^{-1}) with a total volume of 150 ml. There are small contributions from ventricles' ependymal cell linings, and even smaller quantities from fluid leaking into the perivascular spaces (blood-brain barrier [BBB] leakage).[1,6]

CSF production is also under the influence of the circadian rhythm, with the peak production of CSF occurring during sleep. CSF reabsorption occurs primarily via the arachnoid granulations present in the dural sinuses into the venous circulation. A smaller proportion of CSF gains access to the cerebral venous system by transependymal flow and is absorbed in nerve root sleeves via lymphatics.[3,9]

The blood-brain barrier (BBB)

A term commonly used to describe a barrier of tight junctions between capillary endothelial cells in the brain and epithelial cells in the choroid plexus, effectively preventing the movement of ionised substances and those with higher molecular weights.[9] It allows free passage of lipid-soluble molecules (most anaesthetics), oxygen, and carbon dioxide, whereas most ions, proteins, and large substances (like mannitol) penetrate poorly. Water moves freely across the BBB due to bulk flow. Acute plasma hypertonicity results in a net movement of water out of the brain, whereas acute hypotonicity causes a net movement of water into the brain. Severe hypertension, tumours, trauma, strokes, infection, and marked hypercapnia can disrupt the BBB.[6]

Pathological states and neuroprotection

The concept of neuroprotective intervention encompasses therapies that favourably shift the balance of cerebral oxygen supply and utilisation, as well as those that prolong survival in ischemic states. In addition to impacting the delivery of oxygen and nutrients to metabolically active neurons, alteration of cerebral vessel dynamics by anaesthetic agents can influence the tissue composition encountered during neurosurgical intervention.[3]

Ischaemic brain injury is classified as global (complete) or focal (incomplete). Global ischaemia includes total circulatory arrest, e.g. cardiac arrest, as well as global hypoxia, e.g. severe respiratory failure, drowning, and asphyxia. Focal ischaemia includes embolic, haemorrhagic, and atherosclerotic strokes, as well as blunt, penetrating, and surgical trauma.[6]

In brain-injured patients, the integrity of the BBB is often impaired, and the vasoactive neurotransmitters released produce marked changes in CBF and ICP. In these patients, autoregulation is impaired and CBF depends on CPP for adequate supply. However, the CPP in an injured brain is variable within different regions of the brain and varies with time after injury. The Brain Trauma Foundation recommends a target CPP of 50–70 mmHg for TBI.[1] With focal ischaemia, the brain tissue surrounding a severely damaged area may suffer marked functional impairment but remain viable, this area is known as the ischaemic penumbra. If further injury is limited, and normal flow is rapidly restored, these areas may recover completely.

Table II: Comparative effects of anaesthetic agents on cerebral physiology[19]

Agent	CMR	CBF	CSF Production	CSF Absorption	CBV	ICP
Halothane	↓↓	↑↑↑	↓	↓	↑↑	↑↑
Isoflurane	↓↓↓	↑	±	↑	↑↑	↑
Desflurane	↓↓↓	↑	↑	↓	↑	↑
Sevoflurane	↓↓↓	↑	?	?	↑	↑
Nitrous oxide	↓	↑	±	±	±	↑
Barbiturates	↓↓↓↓	↓↓↓	±	↑	↓↓	↓↓↓
Etomidate	↓↓↓	↓↓	±	↑	↓↓	↓↓
Propofol	↓↓↓	↓↓↓↓	?	?	↓↓	↓↓
Benzodiazepines	↓↓	↓	±	↑	↓	↓
Ketamine	±	↑↑	±	↓	↑↑	↑↑
Opioids	±	±	±	↑	±	±
Lidocaine	↓↓	↓↓	?	?	↓↓	↓↓

[1]↑, increase; ↓, decrease; ±, little or no change; ?, unknown; CMR, cerebral metabolic rate; CBF, cerebral blood flow; CSF, cerebrospinal fluid; CBV, cerebral blood volume; ICP, intracranial pressure.

The aims to prevent or limit neuronal tissue damage are the same for both focal and global ischaemia. Clinical goals are to optimise CPP, decrease metabolic requirements (basal and electrical), possibly block mediators of cellular injury, and restore perfusion and oxygenation. CBF is normally reduced in the first 24 hours after brain injury and normocapnia (33–40 mmHg) should be maintained because hypocapnia will further decrease CBF and risk cerebral ischaemia. Therefore, hyperventilation with hypocapnia should be strictly avoided.[3] Hyperoxia can be detrimental and worsen neurological injury by releasing oxygen-free radicals, and brain-injured patients have the best outcome when systemic normoxia is maintained. Oxygen delivery should be titrated to generate an arterial oxygen saturation of 94–96%. In the presence of cerebral vasospasm, induced hypertension may help improve CBF. Prolonged episodes of increased cerebral metabolism, such as during seizures, can result in permanent neurological damage and should be dealt with immediately.[6]

Hypothermia is an effective way of protecting the brain during focal and global ischaemia. It decreases both basal and metabolic requirements throughout the brain. Additionally, hypothermia reduces free radicals and other mediators of ischaemic injury. Induced hypothermia is beneficial following cardiac arrest.[3,6]

Nimodipine plays a role in the treatment of vasospasm associated with subarachnoid haemorrhage. A dihydropyridine-type calcium-channel blocker is thought to reduce vasospasm by blocking calcium influx into ischaemic cells, preventing apoptosis of those cells. There was evidence of improved functional outcome but no angiographic vasospasm as Nimodipine was found to lower the incidence of adverse reactions and improve the prognosis of patients.[3,6]

Effect of anaesthetics on cerebral blood flow (CBF) and metabolic rate

Anaesthetic drugs cause dose-related and reversible alterations in many aspects of cerebral physiology, including CBF, CMR, and electrophysiological function (EEG, evoked responses) (Table II). The delivery of energy substrates is dependent on CBF, and modest alterations in CBF can influence the neuronal outcome substantially in the setting of ischemia. Control and manipulation of CBF are central to the management of ICP because as CBF varies in response to vasoconstrictor-vasodilator influences, and CBV varies with it. Conversely, the effects of general anaesthesia on CBF and CMR can be altered to improve both the surgical course and the clinical outcome of patients with neurological disorders.[3,18]

Several anaesthetics, including barbiturates, isoflurane, sevoflurane, desflurane, propofol, and etomidate, increase plasma concentrations causing progressive suppression of EEG activity and a concomitant reduction in the CMR. However, increasing the plasma level beyond what is required to first achieve suppression of the EEG results in no further depression of the CMR. The component of the CMR required for the maintenance of cellular integrity, the "housekeeping" component, is unaltered by anaesthetic drugs.[18]

Conclusion

Cerebral physiology encompasses many complex, yet understandable concepts, and every physician needs to have a good grasp of these concepts. Furthermore, it forms the basis for the management of patients undergoing intracranial surgery or who need neurocritical care.

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References

1. Tameem A, Krovvidi H. Cerebral physiology. BJA Education. 2013;13(4):113-8. https://doi.org/10.1093/bjaceaccp/mkt001.
2. Slupe AM, Kirsch JR. Effects of anesthesia on cerebral blood flow, metabolism, and neuroprotection. J Cereb Blood Flow Metab. 2018;38(12):2192-208. https://doi.org/10.1177/0271678X18789273.
3. Drummond JC, Patel PM. Cerebral physiology and the effects of anesthetics and techniques. In: Miller RD, Cucchiara RF, Miller ED, et al., editors. Anesthesia. 5th ed. Philadelphia: Churchill Livingstone; 2000. p. 695-733.
4. Schoenemann PT. Evolution of the size and functional areas of the human brain. Annual Rev Anthropol. 2006;35:379-406. https://doi.org/10.1146/annurev.anthro.35.081705.123210.
5. Harilall Y, Adam JK, Biccard BM, Reddi A. Correlation between cerebral tissue and central venous oxygen saturation during off-pump coronary bypass graft surgery. Perfusion. 2010;26(2). https://doi.org/10.1177/0267659110387846.
6. Butterworth J, Mackey DC, Wasnick J. Morgan and Mikhail's clinical anaesthesiology. 5th ed. McGraw-Hill Education; 2013. p. 575-88.
7. Safar P. Cerebral resuscitation after cardiac arrest: a review. Circulation. 1986;74(6 Pt 2):138-53.
8. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metab. 2011;14(6):724-38. https://doi.org/10.1016/j.cmet.2011.08.016.
9. Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's review of medical physiology. 23rd ed. McGraw-Hill Medical; 2009. p. 569-77.
10. PHED 301 Students. Advanced anatomy [Internet]. 2nd ed. Pressbooks; 2018. Available from: https://pressbooks.bccampus.ca/advancedanatomy1sted/chapter/nerves-blood-vessels-and-lymph-7/. Accessed on 13 September 2023.
11. Sokoloff L. Anatomy of the cerebral circulation. In: Welch KMA, Caplan LR, Reis DJ, et al., editors. Primer on cerebrovascular diseases. 1st ed. New York: Academic Press; 1997. https://doi.org/10.1016/B978-012743170-3.50002-9.
12. Rostrup E, Knudsen GM, Law I, et al. The relationship between cerebral blood flow and volume in humans. Neuroimage. 2005;24(1):1-11. https://doi.org/10.1016/j.neuroimage.2004.09.043.
13. Figure 3 Erickson KM, Cole DJ. Arterial hypotension and hypertension. In: Brambrink A, Kirsch JR, eds. Neuroanesthesia and Critical Care Handbook. New York: Springer Publishing; 2010.)
14. Figure 4 [Internet]. Available from: https://derangedphysiology.com/main/sites/default/files/sites/default/files/CICM%20Primary/F%20Respiratory%20system/relationship%20of%20MAP%2C%20O2%20and%20CO2%20effects%20on%20cerebral%20blood%20flow.jpg.
15. Figure 5 [Internet]. Available from: https://europepmc.org/articles/PMC6282215/bin/10.1177_0271678X18789273-fig1.gif
16. Figure 6 [Internet]. Available from: https://www.researchgate.net/publication/322946615/figure/fig2/AS:590841714331648@1517879050197/Pressure-volume-curve-for-ICP-The-pressure-volume-curve-has-four-zones-1-baseline.png.
17. Figure 7 [Internet]. Available from: https://emcrit.org/ibcc/evd/attachment/evdwaveforms/.
18. Patel P, Drummond JC. Cerebral physiology and the effects of anesthetic drugs. 2010;1:594-674. https://doi.org/10.1016/B978-0-443-06959-8.00013-3.
19. Table II [Internet]. Available from: https://img.brainkart.com/imagebk28/ioGCAeT.jpg.

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FCA REFRESHER COURSE

Bernoulli's principle and the Venturi effect

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Keywords: Bernoulli's principle, Venturi effect, fluid mechanics

Introduction

Bernoulli's principle and the Venturi effect are important theoretical and clinically applicable concepts in fluid mechanics. This article explores the physical principles and clinical application of fluid flow in anaesthetic practice with a particular focus on Bernoulli's principle and equation and the Venturi effect.

Bernoulli's principle

Bernoulli's principle governs the behaviour of fluids along the length of a tube.[1] The principle applies to fluids in either liquid or gaseous states.[2] The principle was published by Daniel Bernoulli (1700–1782), a Swiss physicist and mathematician.[3] Bernoulli's principle states that an increase in the flow velocity of a fluid is accompanied by a concomitant decrease in its pressure and vice versa.[4]

Numerous observations typifying the pressure drop experienced in rapidly moving fluids present themselves in our daily lives. When overtaking a truck with a car on the highway, the car tends to veer towards the truck and this phenomenon is explained by Bernoulli's principle. When a car overtakes a truck, a channel is created, and the velocity of airflow within that channel must increase causing the pressure within the channel to drop. Thus, the pressure on the outside of the two moving vehicles is greater than the pressure within the channel created by the two vehicles, and it is this pressure outside the two vehicles that pushes them together.

Bernoulli's equation

Quantitatively, Bernoulli's principle is expressed as Bernoulli's equation. Bernoulli's equation describes the relationship between the pressure, velocity, and elevation of a moving fluid. Bernoulli's equation states that for an ideal fluid, which is inviscid, incompressible, and flowing along a streamline, the following sum is constant:[5,6]

$$P + \frac{1}{2}\rho v^2 + \rho g h = \text{constant} \quad \text{(Equation 1)}$$

Where: P = pressure, ρ = density of the fluid, v = velocity of the fluid, g = acceleration due to gravity, h = height above a set reference point. The second and third terms in the above equation are the kinetic and potential energy respectively.

It is worth noting that Bernoulli's equation can either be derived from Newton's second law of motion or the work-energy theorem.[5] The derivation of Bernoulli's equation is beyond the scope of this article. However, Bernoulli's equation is the direct application of the law of conservation of energy to an ideal fluid.[5,6]

From Equation 1 it is important to note that if the kinetic energy of the fluid increases, there will be a concomitant fall in either its potential energy or pressure.[4] Bernoulli's equation is useful in determining the flow velocity of a fluid or its pressure along a streamline. If in the Bernoulli equation (Equation 2 expressed below) subscripts 1 and 2 refer to any two points along the streamlined path the fluid follows, the equation becomes:

$$P_1 + \frac{1}{2}\rho v_1^2 + \rho g h_1 = P_2 + \frac{1}{2}\rho v_2^2 + \rho g h_2 \quad \text{(Equation 2)}$$

If it is assumed that the height remains constant and the predominant fluid flow is horizontal, such that potential energy can be ignored, Bernoulli's equation then becomes Equation 3:

$$P_1 + \frac{1}{2}\rho v_1^2 = P_2 + \frac{1}{2}\rho v_2^2 \quad \text{(Equation 3)}$$

The above terms can be rearranged as follows:

$$P_1 - P_2 = \frac{1}{2}\rho v_2^2 - \frac{1}{2}\rho v_1^2 \quad \text{(Equation 4)}$$

$$\therefore \Delta P = \frac{1}{2}\rho\,(v_2^2 - v_1^2) \quad \text{(Equation 5)}$$

Simplified Bernoulli's equation in echocardiography

In echocardiography, the simplified Bernoulli's equation (Equation 8) is routinely used to quantify pressure gradients across valves from measured Doppler velocities.[7] When using Bernoulli's equation in clinical practice, pressure is converted from Pascal to mmHg and the density of blood is assumed to be 1 060kg.m^{-3}.

$$\Delta P \approx \frac{1}{2} \times \frac{1060\ kg.m^{-3}}{133.3\ Pa}\,(v_2^2 - v_1^2) \quad \text{(Equation 6)}$$

$$\therefore \Delta P \approx 4\,(v_2^2 - v_1^2) \quad \text{(Equation 7)}$$

When measuring Doppler velocities across a valve, the distal velocity is greater than the proximal velocity , the difference becomes even greater after squaring the velocities. Consequently, in echocardiography, the second term is often

omitted during calculations resulting in the commonly used and simplified Bernoulli's equation:[7]

$$\Delta P \approx 4 v_2^2 \text{ (Equation 8)}$$

The Venturi effect

A Venturi is a tube with a section of narrowed diameter along its length.[1] The Venturi effect was described by Giovanni Battista Venturi (1746–1822) and it describes the fluid dynamics through a Venturi.[8] The Venturi effect arises because of Bernoulli's principle and thus it is an extension thereof. According to the Venturi effect, when fluid flows through the Venturi its velocity increases leading to a decrease in pressure. Fluid flow exiting the narrowed section and returning to the wider section will then have a decreased velocity with an increased pressure.[1] Figure 1 illustrates the Venturi effect with increasing fluid velocity (v_2) through the narrow constriction. Note the pressure drop at the level of the constriction and the gradual opening of the tube beyond the constriction to maintain streamlined flow (v_1).

Application in anaesthesia

In clinical practice, a Venturi can be applied to a number of devices used in daily anaesthetic practice. These devices with a Venturi design may be used to measure flow or enhance the entrainment of fluids. It is worth noting that the Venturi effect does not describe the entrainment of fluids.[4] Nonetheless, entrainment is a useful practical side effect of the Venturi effect.

The following list of equipment takes advantage of the physical principles of fluid mechanics described by Bernoulli's principle and the Venturi effect. These include pressure restriction valves, flow measurement devices, portable suction units, gas flow nebulisers, high air flow oxygen enrichment (HAFOE) devices, oxygen tents, jet ventilation with a Venturi injector device, carrier gas in an anaesthetic vaporiser, and as a driving gas in a ventilator.[1,9,10] In the section that follows, this article will expound on the applicability of the Venturi effect in HAFOE devices.

It is noteworthy that the mechanism of entrainment by the fixed orifice in a Venturi device and the final delivered fraction of inspired oxygen (F_iO_2) can also be explained by jet mixing.[11] The physical principles behind jet mixing are beyond the scope of this article and the particular focus is on the Venturi effect in explaining the mechanism of air entrainment.

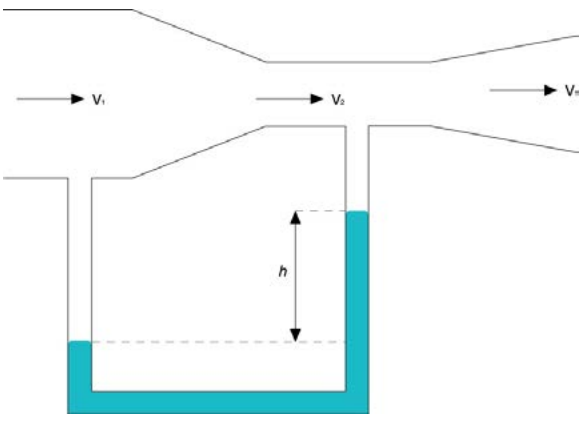

Figure 1: The Venturi effect

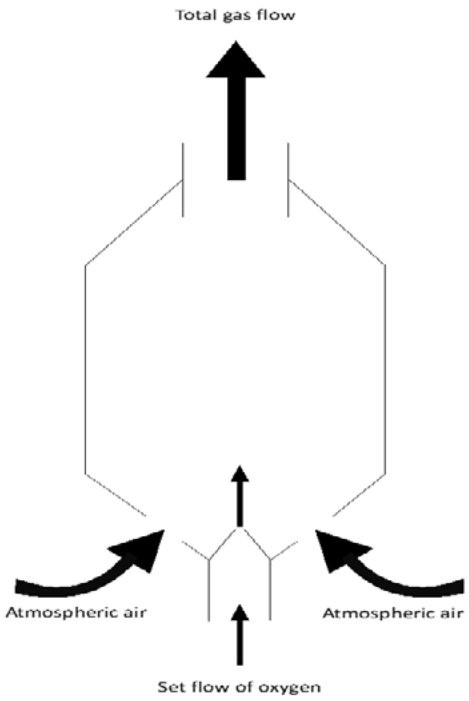

Figure 2: Fixed orifice Venturi device

HAFOE devices

HAFOE devices are air entrainment devices that deliver a constant F_iO_2.[12] HAFOE devices such as the Venturi mask are also known as fixed performance devices. The different fixed orifice Venturi devices are coloured-coded. Figure 2 illustrates a fixed orifice Venturi device. Each colour-coded fixed orifice Venturi device states the required oxygen flow to deliver the specified F_iO_2. On the sides of the fixed orifice Venturi device are apertures that allow the entrainment of atmospheric air.

A set flow of oxygen is delivered across the constriction, atmospheric air is entrained through the side apertures. This results in a higher total gas flow with a lower oxygen concentration.

The concentration of the final delivered F_iO_2 is independent of the flow rate and dependent on the entrainment ratio.[8] For example, a 40% fixed orifice Venturi device has an air-to-oxygen entrainment ratio of 3:1. Thus, a set flow of 8 l/min delivers a total flow of 24 l/min. However, more atmospheric air can be entrained if the patient's peak inspiratory flow rate exceeds the total gas flow supplied by the fixed orifice Venturi device, leading to a further dilution of the final delivered F_iO_2.[12]

To calculate the air-to-oxygen entrainment ratio, the following equation can be used:[8]

$$Entrainment\ ratio = \frac{Entrained\ flow}{Driving\ flow}$$

Conclusion

Bernoulli's principle and the Venturi effect are the cornerstone concepts that govern how fluids behave in a system. These concepts are leveraged in daily anaesthetic practices to provide optimal care to patients during the perioperative period.

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References

1. Aitkenhead AR, Moppett IK, Thompson JP. Smith and Aitkenhead's textbook of anaesthesia. 6th ed. United States: Churchill Livingstone Elsevier; 2013. p. 244-311.
2. Srivastava A, Sood A, Joy SP, Woodcock J. Principles of physics in surgery: the laws of flow dynamics physics for surgeons - part 1. Indian J Surg. 2009;71(4):182-7. https://doi.org/10.1007/s12262-009-0064-x.
3. Badeer HS. Hemodynamics for medical students. Adv Physiol Educ. 2001;25(1-4):44-52. https://doi.org/10.1152/advances.2001.25.1.44.
4. Cross ME, Plunkett EVE. Physics, pharmacology and physiology for anaesthetists: key concepts for the FRCA. 2nd ed. United Kingdom: Cambridge University Press; 2014. p. 38-9. https://doi.org/10.1017/CBO9781107326200.
5. Ling SJ, Sanny J, Moebs W. University physics volume 1 [Internet]. Houston: OpenStax; 2021. p. 696-701. Available from: https://openstax.org/books/university-physics-volume-1/pages/1-1-the-scope-and-scale-of-physics.
6. Walker J. Fundamentals of physics: Halliday & Resnick. 10th ed. United States: Wiley; 2014. p. 401-12.
7. Savage RM, Aronson S. Basic perioperative transesophageal echocardiography: a multimedia review. 1st ed. Philadelphia: Lippincott Williams & Wilkins; 2013. p. 169-70.
8. Gilbert-Kawai ET, Wittenberg MD. Essential equations for anaesthesia: key clinical concepts for FRCA and EDA. 1st ed. United Kingdom: Cambridge University Press; 2014. p. 26-7. https://doi.org/10.1017/CBO9781139565387.
9. Ehrenwerth J, Eisenkraft JB, Berry JM. Anesthesia equipment: principles and applications. 2nd ed. Philadelphia: Elsevier Saunders; 2013. p. 576.
10. Dorsch JA, Dorsch SE. Understanding anesthesia equipment. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2008. p. 666-83.
11. Dobson MB. Use of jet mixing devices with an oxygen concentrator. Thorax. 1992;47(12):1060-2. https://doi.org/10.1136/thx.47.12.1060.
12. Marino PL. Marino's the ICU book. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2014. p. 434.

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FCA REFRESHER COURSE

The microcirculation

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The microcirculation is a network of complex vascular structures consisting of arterioles, capillaries, and venules unique to each organ it supports. It is essential for the delivery of oxygen and nutrients to cells and the removal of waste for eventual metabolism and excretion.

The microcirculation's anatomical complexity is matched by its numerous physiological functions, which are not limited to its role in the inflammatory response, neurotransmitter functions, and coagulation. With the advancement of technology, we have come to appreciate this unique network and its influences on multiple systems. Its effects on perfusion can now be monitored and visualised to influence decision-making and alter clinical judgement continuously throughout any intervention or management. The need to monitor it independently from the macrocirculation has also been established, as certain disease states can lead to a lack of coherence in the two networks.

Although we have learnt much about the microvascular network and its influence on the anaesthesiologist's management of patients, we are yet to determine if closer monitoring of the microvasculature will lead to better patient outcomes.

Keywords: microcirculation, complex vascular structures

Introduction

History

The description of microcirculation goes back as far as the 16th century when Janssen invented the compound microscope.[1] By then, the microcirculation was already at the centre of inflammatory response discussions.[1] The 20th century proved to be the time of greatest development in the understanding of the microcirculation.[1] During this period, the microcirculation was depicted in vivo and was investigated for its role in inflammation and coagulation.[1]

Description

The microcirculation consists of arterioles, capillaries, and venules (Figure 1).[2] It has the largest endothelial surface area in the body.[2] These endothelial cells are teeming with receptors that allow communication within and across organs.[2] The vessels involved can span from 5 to 200 micrometres in diameter.[2] The vessels in this network are embedded in organs.[2] As such, the architectural structure of the microcirculation is unique to each organ and its requirements.[2]

The surrounding lymphatic network is also depicted in Figure 1, as well as the supporting vascular smooth muscles and nerve fibres associated with the microvasculature in many organs.[3]

The microcirculation and its role in physiology

Arterioles are the smooth and skeletal muscle-containing component of the microcirculation.[2] This anatomy allows them to regulate blood flow and monitor vascular wall shear stress.[2] Sympathetic nerve fibres cue the vasoconstriction and vasodilation of arterioles with the release of neurotransmitters (norepinephrine) that act on vascular smooth muscle.[2] Coordinated constriction and dilatation is made possible by gap junction communication across endothelial cells.[2] The Hagen-Poiseuille law allows us to appreciate the significance of the change in the radius of this vessel network and its influence on blood flow to tissues.[2] Therefore, it is not surprising to learn that this network of vessels is responsible for 80% of pressure drop in the body.[2]

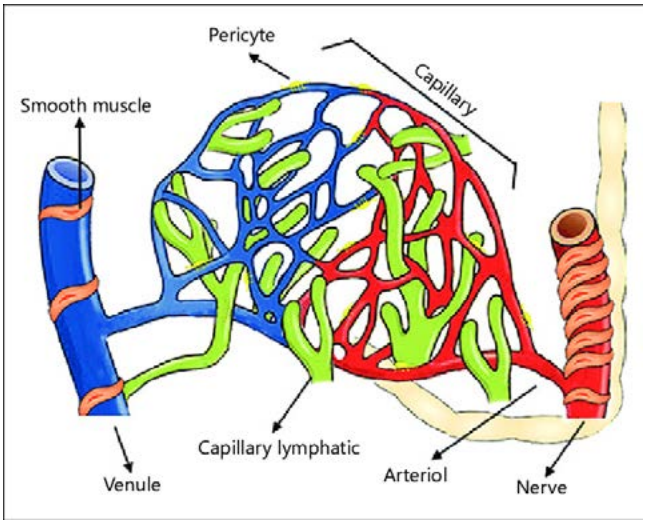

Figure 1: Illustration of the microvascular network consisting of arterioles, venules, and capillaries

The arteriole tone is regulated by myogenic, neurohormonal, and metabolic mechanisms.[3] Meanwhile, capillaries are central to the diffusion of cell nutrients to the interstitial tissue and gaseous exchange.[2] Because they lack smooth muscle, they cannot constrict and dilate.[2] The capillary surface area is approximately 70 m^2 in an adult human.[3] The capillary wall houses the endothelial glycocalyx on the luminal side.[2] The glycocalyx consists of proteoglycans, glycoproteins, and glycosaminoglycans.[3] The glycocalyx is involved in homeostasis, solute transport, immunological mechanisms, and haemostasis.[3] Venules smaller than 50 micrometres in diameter also do not contain smooth muscle or skeletal muscle tissue.[2] Instead, they contain receptors that partake in ligand binding to rheological cell lines.[2]

The microcirculation ultimately plays a significant role in oxygen transport by convection of oxygen-carrying red blood cells and oxygen diffusion.[2] It is also central to nutrient delivery, solute exchange and diffusion of hormones and neurotransmitters, and waste removal.[2] Given the significant function it fulfils in multiple systems and organs, it is an important component to monitor.

Monitoring the microcirculation

Advances in haemodynamic monitoring have assisted anaesthesiologists with macrocirculation management and manipulation. The microcirculation, however, proves difficult to monitor.[4] In certain disease states, the coherence of the macrocirculation and microcirculation is compromised, making it difficult to rely on macrocirculation-based parameters for monitoring.[4]

Handheld vital microscopes

The handheld microscope has a ring of light-emitting diodes, the light wavelength of 530 nm is absorbed by red blood cells allowing one to visualise the flow of red blood cells.[5] This imaging of red blood cells can occur at any mucosal surface that contains microcirculation.[5] There are currently three generations of handheld microscopes, with debulking and changes in image quality improving the technology with each generation.[4] This non-invasive technique has gained popularity in the critical care space and is commercially available.[5]

Studies have demonstrated that sublingual microcirculatory changes mirror changes in the microcirculation of other major organs.[4] This has allowed the extrapolation of the microcirculatory condition using handheld microscopes, viewing sublingual microvasculature.[4] The microvascular images obtained allow quantification of measures, such as microvascular flow index, which looks at the gross impression of red blood cell velocity, perfused vessel density determined by capillary distance, and red blood cell velocity and heterogeneity index, which looks at the heterogeneity of blood flow in different regions.[5]

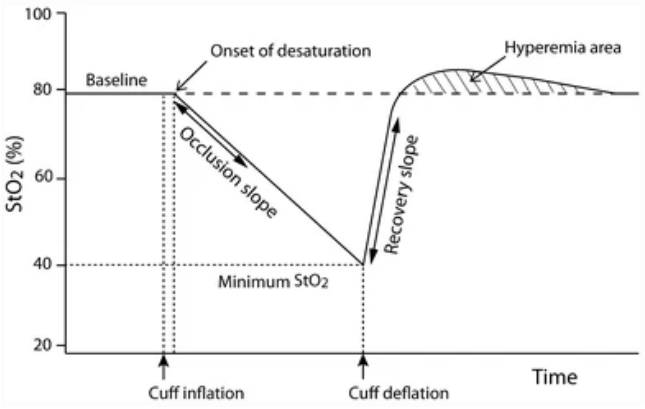

Figure 2: The changes in saturation during vascular occlusion and reperfusion[6]

Vascular occlusion test

The vascular occlusion test uses a pneumatic cuff over the arm to induce transient ischaemia.[5] An oxygen sensor of the thenar muscles monitors changes in tissue oxygen saturation.[5] The parameter changes are then plotted on a graph and the recovery slope, indicating the amount of time it takes for tissue oxygenation to normalise after ischaemia, is used to predict patient outcome after major surgery (Figure 2).[5]

Laser Doppler flowmetry

This technique measures backscattered light that is Doppler-shifted during tissue motion.[5] A two-dimensional image is created from different skin sources.[5] However, this technique is not accurate if there is a lack of vascular heterogeneity, and it is limited in its ability to monitor alterations in microvasculature.[5]

Near-infrared spectroscopy

This non-invasive technique uses the difference in absorption of light at two wavelengths (600 nm and 800 nm) by deoxyhaemoglobin to determine haemoglobin saturation in the tissue under study.[7] This technique can be used alongside a vascular occlusion test to determine the recovery of tissue oxygenation post-ischaemia.[7]

Sublingual capnometry

The partial pressure of carbon dioxide in sublingual tissue can be monitored using a microelectrode sensor.[8] The difference between arterial and tissue carbon dioxide partial pressure is measured.[8] A decrease in the pressure gap suggests an improvement in capillary perfusion.[8] Gastric mucosal-arterial partial pressure carbon dioxide has also been used in a similar way to monitor microcirculation.[8]

Gastric tonometry

Gastric tonometry has been used to measure the condition of the splanchnic circulation.[9] Decreased perfusion leads to increased partial pressure of carbon dioxide in gastric mucosa, which in turn leads to a reduction in gastric pH.[9] A semipermeable balloon

is attached to a nasogastric tube and inserted into the stomach.[9] The balloon is filled with saline and the carbon dioxide is allowed to diffuse across the membrane.[9] The partial pressure of carbon dioxide in the saline is then measured and the Henderson-Hasselbalch equation is used to quantify the pH.[9] The difference between the gastric mucosal-arterial pH is used to demonstrate the degree of gastric ischaemia.[9]

Anaesthesia and the microcirculation

Anaesthetists have a special interest in manipulating microcirculatory properties in their physiological and pathological states to influence the flow of blood to tissue for resultant oxygenation. Administered anaesthesia also alters the microcirculation, potentially influencing patient outcomes. The discussion below explores the various influences disease and anaesthesia have on microcirculation.

The microcirculation and fluid administration

Fluid administration has long been identified as an essential part of resuscitation for many states of shock. Early fluid administration in sepsis and patients with a microvascular flow index of less than 2.6 has been found to improve the flow index in the microcirculation.[10] However, in patients where the microvascular flow index was greater than 2.6, there was no improvement in flow index and therefore no advantage in fluid administration.[10]

The microcirculation in sepsis

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to infection.[11] It results in microcirculatory dysfunction due to endothelial dysfunction, shedding of the glycocalyx, and abnormal secretion of neurotransmitters involved in vasodilation and vasoconstriction.[4] Not only is there a compromise in nutrient tissue delivery, but the tissue itself also has a reduced ability to extract and utilise oxygen and nutrients appropriately.[11] The microvascular changes that precede these events are changes in capillary wall density, blood flow shunts, and rheological changes leading to microthrombi.[11] Sepsis is recognised as a disease state where the macrocirculation and the microcirculation are uncoupled.[11] Consequently, the monitoring of microcirculation in sepsis has grown popular.[11] This improved monitoring is yet to prove more useful at bettering outcomes in septic patients.

The microcirculation in non-cardiac surgery

Surgical response

A meta-analysis has shown that there are significant changes in microcirculatory flow immediately after surgery using microvascular flow index and perfusion vessel density as monitored parameters.[12]

Intravenous induction agents

Propofol, thiopentone, and ketamine cause vasodilation by inhibiting L-type gated calcium channels.[13] Propofol has been shown to induce a reduction in microvascular density and capillary perfusion in ASA 1 patients through vasodilation.[13] Propofol has also been shown to have anti-inflammatory effects in humans by altering the balance of cytokine and anti-inflammatory interleukins.[13] A small study also showed improvement in vascular occlusion test recovery time as a result of peripheral vasodilation after induction of anaesthesia with a total intravenous technique, suggesting that microcirculation monitoring may be a poor indicator of microvascular status at induction.[14] These changes are yet to be correlated with patient outcomes.[12]

Inhalation agents

Volatile agents cause dose-dependent smooth muscle tone reduction in the arterioles.[15] This causes a change in blood flow across microcirculatory vasculature.[15] These agents also contribute to blocking sympathetic outflow and preventing an appropriate adrenergic response to reduction in cardiac output.[15] Sevoflurane, isoflurane, and desflurane have been shown to reduce the amount of pro-inflammatory cytokines and tumour necrosis factor production in humans.[13]

Neuraxial technique

Thoracic epidural anaesthesia has been shown to improve splanchnic blood flow, thereby improving gastric mucosal pH.[13] However, epidural anaesthesia limited to the lumber region has been shown to cause splanchnic vasoconstriction due to the compensatory increase in sympathetic outflow at the thoracic level.[13]

Vasopressors

In a pathological state such as sepsis, loss of macrovascular and microvascular coherence is common.[16] The use of vasopressors, such as norepinephrine, can increase macrovascular parameters, such as mean arterial pressure, left and right ventricular stroke work indices, and cardiac index while failing to improve the sublingual microvascular flow index.[16]

The microcirculation in cardiac surgery

There are many changes in the microcirculation as a result of cardiac surgery and all it entails.[17] Cardiopulmonary bypass, hypothermia and ischaemic reperfusion can all contribute to microvascular dysfunction leading to microthrombi formation, poor oxygen delivery, and changes in neurohormonal activity that regulates vessel wall size and red blood cell convective flow across the vessels.[17] The above results in poor microcirculatory flow and possibly, poor tissue perfusion.[17]

Conclusion

The microcirculation is a complex network involved in all organ systems. It is key to many physiological functions and is significantly affected by anaesthesia. The anaesthetist's awareness of its complexity and monitoring options may be the key to improved patient outcomes. The use of various drugs targeted at improving macrocirculation might have limited use in improving microcirculation in disease states that lead to the uncoupling of these vascular networks. It is prudent to identify the patients at risk of this uncoupling and adjust the targeted monitoring and treatment accordingly.

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References

1. Granger DN, Senchenkova E. Historical perspectives [Internet]. In: Inflammation and the microcirculation. San Rafael: Morgan & Claypool Life Sciences; 2010. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53379/.
2. Popel AS, Johnson PC. Microcirculation and hemorheology. Annu Rev Fluid Mech. 2005;37:43-69. https://doi.org/10.1146/annurev.fluid.37.042604.133933.
3. Guven G, Hilty MP, Ince C. Microcirculation: physiology, pathophysiology, and clinical application. Blood Purif. 2020;49(1-2):143-50. https://doi.org/10.1159/000503775.
4. Kara A, Akin S, Ince C. Monitoring microcirculation in critical illness. Curr Opin Crit Care. 2016;22(5):444-52. https://doi.org/10.1097/MCC.0000000000000335.
5. Nam K, Jeon Y. Microcirculation during surgery. Anesth Pain Med (Seoul). 2022;17(1):24-34. https://doi.org/10.17085/apm.22127.
6. Cho YJ, Bae J, Kim TK, et al. Microcirculation measured by vascular occlusion test during desflurane-remifentanil anesthesia is superior to that in propofol-remifentanil anesthesia in patients undergoing thoracic surgery: subgroup analysis of a prospective randomized study. J Clin Monit Comput. 2017;31(5)989-97. https://doi.org/10.1007/s10877-016-9937-2.
7. Futier E, Christophe S, Robin E, et al. Use of near-infrared spectroscopy during a vascular occlusion test to assess the microcirculatory response during fluid challenge. Crit Care. 2011;15(5):R214. https://doi.org/10.1186/cc10449.
8. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL. Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med. 2006;32(4):516-23. https://doi.org/10.1007/s00134-006-0070-4.
9. Dries DJ. Chapter 28 - traumatic shock and tissue hypoperfusion: nonsurgical management. In: Parrillo JE, Dellinger, editors. Critical care medicine. 3rd ed. Mosby; 2008. p. 521-44. https://doi.org/10.1016/B978-032304841-5.50030-3.
10. Pranskunas A, Koopmans M, Koetsier PM, Pilvinis V, Boerma EC. Microcirculatory blood flow as a tool to select ICU patients eligible for fluid therapy. Intensive Care Med. 2013;39(4):612-9. https://doi.org/10.1007/s00134-012-2793-8.
11. Ince C, De Backer D, Mayeux PR. Microvascular dysfunction in the critically ill. Crit Care Clin. 2020;36(2):323-31. https://doi.org/10.1016/j.ccc.2019.11.003.
12. Chalkias A, Papagiannakis N, Mavrovounis G, et al. Sublingual microcirculatory alterations during the immediate and early postoperative period: a systematic review and meta-analysis. Clin Hemorheol Microcirc. 2022;80(3):253-65. https://doi.org/10.3233/CH-211214.
13. Turek Z, Sykora R, Matejovic M, Cerny V. Anesthesia and the microcirculation. Semin Cardiothorac Vasc Anesth. 2009;13(4):249-58. https://doi.org/10.1177/1089253209353134.
14. Kim TK, Cho YJ, Min JJ, et al. Tissue microcirculation measured by vascular occlusion test during anesthesia induction. J Clin Monit Comput. 2016;30(1):41-50. https://doi.org/10.1007/s10877-015-9679-6.
15. Vollmar B, Habazettl H. Organ blood flow and microcirculation during inhalation anaesthetics. Baillière's Clin Anaesth. 1993;7(4):961-90. https://doi.org/10.1016/S0950-3501(05)80157-6.
16. Dubin A, Pozo MO, Casabella CA, et al. Increasing arterial blood pressure with norepinephrine does not improve microcirculatory blood flow: a prospective study. Crit Care. 2009;13(3):R92. https://doi.org/10.1186/cc7922.
17. Den Os MM, van den Brom CE, van Leeuwen ALI, Dekker NAM. Microcirculatory perfusion disturbances following cardiopulmonary bypass: a systematic review. Crit Care. 2020;24(1):218. https://doi.org/10.1186/s13054-020-02948-w.

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FCA REFRESHER COURSE

Anaesthetic workstation

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Keywords: anaesthetic workstation, gas supply, breathing circuit, ventilators

Introduction

Anaesthesia aims to provide an environment where the surgeon has the best possible surgical conditions and the patient remains comfortable, safe, and pain-free.

The anaesthetic machine is the central component that facilitates monitoring of physiological functions, precisely delivering oxygen and volatile anaesthetic to the patient and eliminating carbon dioxide and excess gas from the system. A ventilator provides support in cases where the patient cannot maintain adequate minute ventilation through spontaneous breathing.

The functional anatomy of the anaesthetic delivery system

Gas supply[1-4]

The anaesthetic machine has a dual gas supply. The primary source of oxygen, medical air, and nitrous oxide is through the central pipeline system. For safety reasons, there must always be a backup source of oxygen. The backup source is provided by oxygen cylinders mounted at the back of the anaesthetic workstation. The gas supply system is divided into three sections depending on the pressure of the gases in each section (see Figure 1: Gas supply to the anaesthetic workstation).

High-pressure system[1,2,4,5]

The oxygen E-cylinder supplies oxygen at a very high pressure. A full E-cylinder has a gauge pressure of around 137 bar (or 2 000 psig) and an oxygen volume of 660 litres. The pressure decreases as the E-cylinder is depleted and can be used to determine how much oxygen is still available in the cylinder. A high-pressure reduction valve is located between the cylinder and the machine, so the pressure reaching the intermediate pressure system is around three bar or 45 psig.

The pin index safety system (PISS) is a safety feature that ensures the correct line connection to the correct cylinder. Each type of gas cylinder head has holes arranged in a specific configuration. Each gas's yoke assembly has metal pins arranged in the same mirror configuration as on the cylinder head. The metal pins must fit into the corresponding holes to create an effective seal. This prevents the accidental connection of the wrong pipe to the wrong gas cylinder.

Intermediate pressure system[1, 2, 4]

This part of the circuit starts after the high-pressure regulator from the cylinders and includes all the pipes from the pipelines and ends with the secondary pressure regulators.

Pipeline gases are delivered at an intermediate four-bar pressure (55 psig). The pressure difference between oxygen from the pipeline and the pressure of three bar in the cylinder line means that oxygen will preferentially come from the pipeline unless its pressure drops below the three bars in the cylinder line. Secondary pressure regulators are present in the lines to reduce the pressure further before the gas reaches the flowmeters.

Safety mechanisms are in place to prevent the delivery of a hypoxic mix to the patient. The first level of protection is the diameter index safety system (DISS). Every piped gas terminates in a specific size and shape connection and is colour-coded. The pipes that carry the gases to the machine are also colour-coded, and they have specific size and shape connectors corresponding to those on the pendant.

An oxygen supply sensor is part of the intermediate pressure system before the secondary pressure regulators. The alarm is triggered when there is a decrease in the pressure within the oxygen line, indicating an oxygen supply failure. Notably, the sensor is present in the pipe where pipeline oxygen and oxygen from the cylinder have already been combined. If the oxygen cylinder is left open, the oxygen failure alarm will not alert the anaesthetist about low pipeline pressure but will only sound once the oxygen in the cylinder is depleted. It is thus essential to close the cylinder when pipeline oxygen is used.

When the oxygen supply dwindles, a valve in the system will reduce or terminate the flow of other gases in the system. This valve is sometimes called a "fail-safe" valve. Since the pressure in the system influences this valve, it may lose its protective function if another gas pressurises the oxygen line.

The oxygen flush bypasses the vaporiser and can deliver 100% oxygen between 35 and 75 litres per minute. It is used to flush

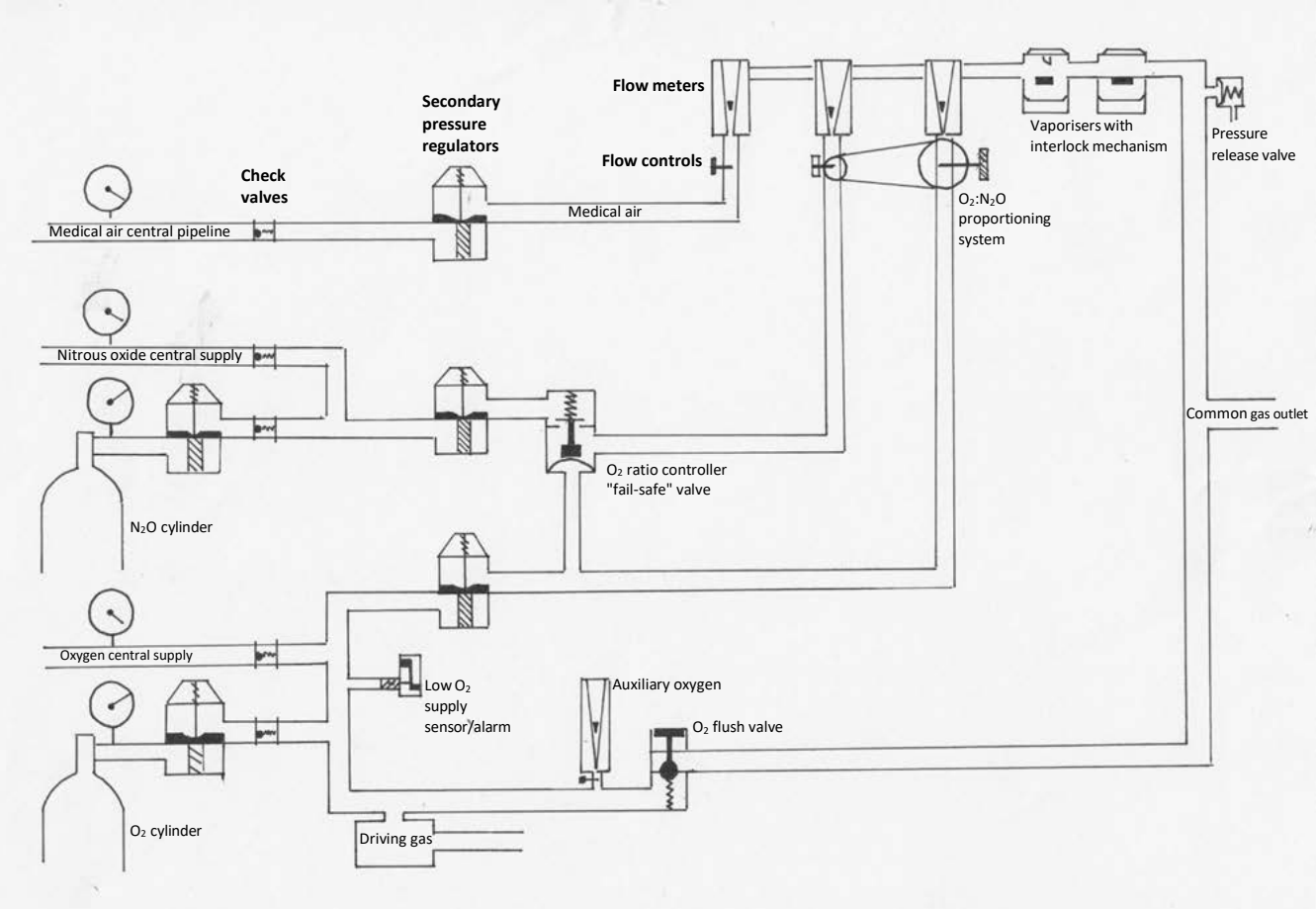

Figure 1: Gas supply to the anaesthetic workstation

the system in case of a leak or to rapidly increase the oxygen concentration in the system. The high flow rate can cause barotrauma if the oxygen flush is used during the inspiratory phase. A decoupling mechanism can negate this risk.

Some machines have an auxiliary oxygen flow meter on the oxygen line that bypasses the vaporiser. This oxygen port can provide oxygen even when the machine is not switched on.

Low-pressure system

The low-pressure system starts at the secondary pressure reduction valves and extends to the fresh gas outlet. The different gases join a common manifold that leads to the vaporisers. The anaesthetist determines the composition and volume of the final gases reaching the fresh gas outlet through the differential selection of the flow rates for the various gases, as well as the proportion of the gas that passes through the vaporiser.

Gases enter the low-pressure system and pass through an oxygen-nitrous oxide proportioning system. This device can be mechanical, electronic, or pneumatic. In mechanical devices, a chain connects the oxygen and nitrous oxide control knobs so that an increase in nitrous oxide will increase oxygen, and a decrease in oxygen will result in a decrease in nitrous oxide. Electronic devices use a paramagnetic analyser to continuously monitor the concentration of gases and to electronically regulate the flow of nitrous oxide relative to oxygen. A pneumatic device works on the balance of the O_2 and N_2O pressure. There is a resistor in both the oxygen and the nitrous pipelines. The resistor in each line causes back-pressure on a diaphragm. A connector shaft separates the oxygen and nitrous diaphragms. The connector shaft controls a "slave valve" in the nitrous line. If the O_2 pressure drops, the back-pressure on the O_2 diaphragm reduces, and a valve moves into the N_2O orifice to reduce or halt the flow.

The flow meters can be physically tapered glass tubes or displayed electronically. Each glass flowmeter must be calibrated for its specific gas, as the flow of each gas depends on density and viscosity. A float is present within each flowmeter. Its diameter is slightly smaller than the narrowest part of the tube. The space between the tube and the float is known as the annular space. As flow increases, it exerts an upward pressure on the float. A gravitational force on the float counteracts the upward pressure. The float will hover at the level where the two forces are in equilibrium. The top of the float indicates the flow rate on a calibrated scale in the tube. At low flows, the flow around the float is laminar and dependent on the viscosity of the gas. At higher flows, the flow around the float becomes turbulent, and its behaviour depends on the gas density.

The outlets of the different flowmeters lead to a common manifold that carries gas towards the vaporiser. The flowmeters join this manifold sequentially. Traditionally, the flowmeters have

been very fragile and the glass of the tubes could break. Should this go undetected, the gases that join the manifold proximally can escape through the broken glass, decreasing its flow in the distal part of the manifold. The concentration of the last gas to be added will then be higher than what is set. Since all the hypoxic safeguards are proximal to this point, this situation can go undetected unless the oxygen analyser picks up the problem at the patient's end. To make the common gas mixture safer, oxygen should be the last gas added to the common gas flow so that its concentration will be the highest.

Electronic devices continuously measure the gas content, concentration, and flow and digitally display the parameters. The machine then uses microprocessors to make the necessary changes.

Common gas flow

The common gas flow then flows through the anaesthetic vaporiser, where it picks up the vapour of the anaesthetic agent. Vaporisers will not be discussed in this article.

Breathing circuit

The fresh gas flow (FGF) enters the breathing circuit after passing through the vaporisers. Note that the breathing circuit also has an internal component that is not visible to the anaesthetist. Essential prerequisites of the breathing circuit are that it must have a low-resistance conduit with a reservoir that matches the patient's minute volume and a conduit to vent waste gas. The most used circuit in anaesthesia is the circle system.

Gas flow in a pipe is influenced by various factors that can be explained by Hagen-Poiseuille's and Ohm's laws.[6]

Ohm's law: $R = {}^{\Delta P}/_{Q}$

Hagen-Poiseuille's law: $\Delta P = {}^{LvV}/_{r^4}$

Regarding Ohm's law, the flow (Q) is directly proportional to the pressure gradient and inversely proportional to resistance. By using Hagen-Poiseuille's law, the pressure difference can be determined. The pressure gradient is directly proportional to the viscosity of the gas (v), the length of the tube (L), and the flow rate (V), and inversely related to the radius (r) to the power of four.

The airway resistance is affected by the type and the rate of the flow. Flow can be laminar, turbulent, or a combination. For laminar flow, Hagen-Poiseuille's law can be used. Therefore, flow moves down the pressure gradient. The flow in the centre of the pipe is faster than the flow rate at the outer core. At high flow rates, laminar flow can also become turbulent.

In contrast, when the flow is turbulent, the particles move randomly in all directions. Turbulent flow occurs at high flow rates or constrictions in the tube. The flow rate is the same throughout the stream. Due to this, the pressure gradient within the pipe increases to maintain forward flow, and resistance also increases. Resistance is directly related to the flow rate squared. To reduce resistance, the length of the circuit should be minimised, the diameter maximised, and any constrictions that can result in turbulent flow must be avoided.

In the case of the circle system, the internal part of the breathing circuit includes the ventilator, the CO_2 absorber canister, the adjustable pressure limiting (APL) valve, and unidirectional valves and sensors to monitor flow, oxygen concentration, and pressure within the breathing circuit.

The CO_2 absorber is critically important in the circle system as the exhaled gas from the patient remains part of the system. The CO_2 must be removed from the system to prevent rebreathing of the CO_2 and diluting the FGF. The reaction in the CO_2 absorber depends on the chemical composition of the absorbent (see Table I).

Soda lime can absorb 26 litres of CO_2 per 100 g of soda lime. The capacity is influenced by the surface area of the absorbent in contact with CO_2, the specific capacity of the different absorbent materials, and the amount of non-saturated absorbent remaining. Smaller particles have a larger surface area compared to larger particles, but it increases the resistance to gases flowing through the canister. The capacity of the absorbent to remove CO_2 may be reduced to 10–20 litres due to various factors not discussed in this article.

A colour change warns the anaesthetist that the absorbent is reaching its capacity. Ethyl violet is added to the absorbent. Adding CO_2 to the absorbent gradually lowers the pH in the canister. Ethyl violet is a colourless substance that changes to violet if the pH decreases below 10.3.[3]

The APL valve is an operator-managed valve that allows gas from the breathing circuit to be vented to the scavenger system. In the fully open position, the patient can breathe spontaneously. When the valve is partially closed, it provides continuous positive airway pressure (CPAP) in the spontaneously breathing patient. When the valve is closed further, it will generate enough positive pressure to allow the anaesthetist to manually provide positive pressure ventilation to the patient.

Table I: Chemical reactions of the CO_2 absorption system[1, 7]

CO_2 reaction with soda lime	
Net reaction: $CO_2 + Ca(OH)_2 = H_2O$ + heat	
Sequential reactions with NaOH as the catalyst: $CO_{2\ (gas)} + H_2O_{\ (liquid)} \rightleftarrows H_2CO_{3\ (aqueous)}$ $H_2CO_3 + 2NaOH \rightarrow Na_2CO_3 + 2H_2O$ + heat $Na_2CO_3 + Ca(OH)_2 \rightarrow CaCO_3 + 2NaOH$ + heat	Sequential reactions with KOH as the catalyst: $CO_{2\ (gas)} + H_2O_{\ (liquid)} \rightleftarrows H_2CO_{3\ (aqueous)}$ $H_2CO_3 + KOH \rightarrow K_2CO_3 + 2H_2O$ + heat $K_2CO_3 + Ca(OH)_2 \rightarrow CaCO_3 + KOH$ + heat
CO_2 reaction with lithium hydroxide monohydrate	
$2LiOH + H_2O + CO_2$ + heat $\rightarrow Li_2CO_3 + 3H_2O$	

Unidirectional inspiratory and expiratory valves are present in the circuit to prevent the backflow of gases within the system. These valves must not get stuck. An expiratory valve stuck in the closed position will cause barotrauma as the expired gases have nowhere to go. An expiratory valve stuck in the open position will result in the inappropriate rebreathing of CO_2.

A reservoir bag forms part of the circuit. The size of the bag is relative to the minute volume required by the patient. A two-litre bag is used for adults, a one-litre bag is available for children, and a 500-millilitre bag is used for babies. As the reservoir bag is the most compliant component of the circle system, it could serve as a protective mechanism against excessive pressure in the system. In combination with the APL valve, it provides a means of manually ventilating the patient. Given its position in the expiratory limb of the circle system, it usually fills with exhaled gases and excess FGF.

An oxygen sensor is placed within the inspiratory limb or Y-piece. This is the last safety check to prevent a hypoxic mixture from being delivered to the patient. The oxygen sensor can be a galvanic fuel cell or a paramagnetic sensor. The latter is used more commonly in newer anaesthetic machines.

Ventilators [1-3, 8]

Ventilators have come a long way since the "iron lung" ventilators used during the polio pandemic. Ventilators today have sophisticated ventilation modes to enable mechanical ventilation to be as physiological as possible. The ventilators on anaesthetic machines generally do not have all the advanced modes available on intensive care ventilators.

Ventilators are classified according to the type of design into bellow-, piston-, and turbine-driven, or according to their power source as pneumatic, electric, or a combination of the two. The position of the ventilator in the circuit depends on the type of ventilator.

Bellows ventilators

Bellows ventilators have a double-circuit system . This means that the driving gas and the fresh gas never mix unless there is a leak in the bellows. A transparent dome covers the bellows, allowing the anaesthetist to observe the movement of the bellows and confirm ventilation visually.

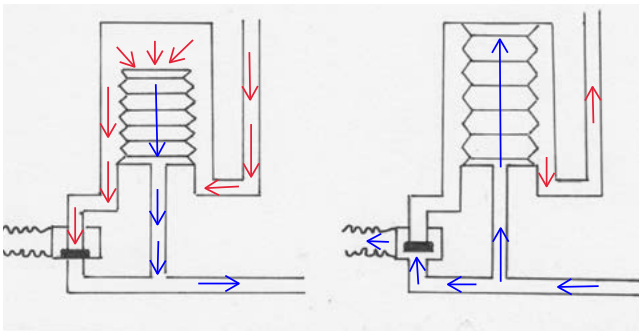

Figure 2: Ascending bellows ventilator

The bellows are filled with the gas components of the FGF, including the volatile agents if those are used. During inspiration, a valve opens that forces the driving gas (usually O_2 or a mixture of O_2 and medical air) into the transparent casing surrounding the bellows. The positive pressure created inside the dome pushes the bellows downwards and displaces the fresh gas in the bellows into the inspiratory limb of the breathing circuit.

The passive recoil of the patient's chest wall during exhalation moves the expired gases into the expiratory limb of the circuit. The return of gases to the ventilator pushes the bellows upwards, and the driving gas that previously filled the dome escapes into the atmosphere. The driving gas does not contain volatile anaesthetics, so the pollution of the operating theatre is not a concern.

The volume of driving gas needed per minute equals the minute volume. Oxygen will be drawn from the cylinder in the event of pipeline failure. The amount of oxygen needed includes both the volume of the driving gas and the volume needed for ventilation of the patient. The volume consumed in the breathing system equals the FGF per minute times the F_iO_2. In this regard, the bellows ventilator will consume oxygen much faster than a piston ventilator and will affect the calculation of the time available before the oxygen cylinder is depleted.

Bellows ventilators are pneumatically driven, but electricity is needed to control the valves that regulate the pneumatic process. The respiratory cycle time and tidal volume are electronically regulated.

Bellows ventilators have a volume sensor in the circuit that detects a change between the set tidal volume and the delivered tidal volume. These sensors provide feedback to the microprocessor to change the volume of the driving gas to offset the change. It takes a few breaths before the set and delivered tidal volumes are similar.

If there is a leak in the breathing system, the ascending bellows will fail to reach the top of the dome after expiration. This safety feature is not available in descending bellows as the weight of the bellows will allow them to reach the bottom even when there is a leak. A leak can thus easily go undetected.

The disadvantages of the bellows ventilator:

- It uses a lot of oxygen to drive the ventilator, this is an undesirable feature in areas where oxygen supplies are limited.
- Presence of auto-positive end-expiratory pressure (auto-PEEP) due to the weight of the bellows.
- A perforation in the bellows can result in barotrauma as the pressurised driving gas will enter the bellows, mix with the fresh gas, and the entire volume will be forced into the lungs; it also dilutes the fresh gas and risks patient awareness or emergence.
- The tidal volume may be inaccurate under certain conditions.
- Fresh gas compensation is needed to avoid excessive tidal volumes at high flows.

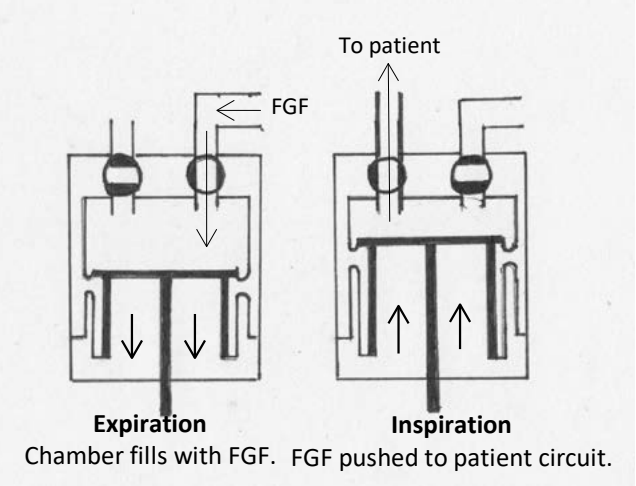

Figure 3: Piston ventilator

Piston ventilators

A piston ventilator is placed within the anaesthetic machine proximal to the unidirectional inspiratory valve. It consists of a cylinder lined with a soft, flexible plastic insert. The piston drive is inside the cylinder. The piston moves backwards and forwards in the cylinder and can be compared to the plunger in a syringe. The distance it moves to deliver the tidal volume is electronically determined, as is the timing of the cycles. A gear system drives the piston forwards and backwards. Backward movement allows the cylinder to fill, while forward movement moves the gas volume into the patient circuit.

The benefits of piston ventilators:

- There is no need for a driving gas to drive the ventilator, making it the preferred ventilator in areas where oxygen is in short supply. In the event of pipeline failure, a lesser volume of oxygen will be drawn from the oxygen cylinder. The calculation of time remaining before the oxygen is depleted is thus only dependent on the FGF.
- More precise delivery of tidal volume.
- More precise control over airway pressure management due to the presence of pressure sensors.
- Oxygen (or medical air) is not vented into the atmosphere, making it more economical.
- Volutrauma is avoided through the fresh gas decoupling mechanism.
- No auto-PEEP.
- Quiet.
- Single circuit system.

The disadvantages of piston ventilators:

- Leaks cannot be visually detected, detection only relies on low-pressure alarms.
- A leak can lead to hypoventilation.
- There is a chance that room air can be entrained when the piston returns to the starting position.

Other types of ventilators include the volume reflector ventilator and the turbine ventilator, which are more commonly used in intensive care ventilators.

The delivered tidal volume on older ventilators was influenced by the FGF. The delivered tidal volume was the sum of the set tidal volume and the FGF. With increased FGF, the anaesthetist had to manually decrease the set tidal volume to avoid volutrauma. Modern machines can keep the tidal volume close to what the anaesthetist sets. The two mechanisms through which this is achieved are fresh gas compensation and fresh gas decoupling.

The mechanism found in the piston and descending bellows ventilators is called fresh gas decoupling. A more accurate name may have been "fresh gas diversion". On inspiration, a valve between the FGF and the ventilator closes, diverting the FGF to the reservoir bag. This prevents the FGF from being added to the tidal volume during inspiration. Gas is drawn from both the reservoir bag and the FGF for the next breath. There is a risk that room air can be entrained into the system if the reservoir bag is not correctly assembled or is absent and the FGF is inadequate.

Ventilators must have alarms to warn about deviations in the system. These alarms include a low and high peak inspiratory pressure alarm, low expired volume alarm, low end-tidal carbon dioxide, and low oxygen supply.

Conclusion

The anaesthetist needs to be familiar with the components of the anaesthetic workstation. Daily tests are essential and knowledge of the system will help find the source of a problem, such as a leak, a circuit pressure problem, etc. It ensures that the workstation works optimally and can deliver a safe anaesthetic to the patient.

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References

1. Bokoch W, Weston S. Inhaled Anesthetics: Delivery Systems. In: Gropper M, Lars I, Eriksson L, et al, editors. Miller's Anesthesia. 9th ed: Elsevier; 2020. p. 572-637. e6.9780323612647.
2. Weston S. Anesthesia Delivery Systems. In: Pardo MJ, editor. Miller's Basics of Anesthesia. 8th ed: Elsevier; 2022. p. 229-52.9780323796774.
3. Brockwell R, Andrews J. Delivery systems for Inhaled Anesthetics. In: Barash P, Cullen B, Stoelting R, editors. Clinical Anesthesia. 5th ed: Lippincott Williams & Wilkens; 2005.0781757452.
4. Loeb R, Eisenkraft J. The Anesthesia Machine and Workstation. In: Ehrenwerth J, Eisenkraft J, Berry J, editors. Anesthesia Equipment Principles and Applications. 3rd ed: Saunders; 2020. p. 25-65.9780323672795. https://doi.org/10.1016/B978-0-323-67279-5.00002-9.
5. Rose G, McLarney JT. Pneumatic Systems. In: Rose G, McLarny J, editors. Anesthesia Equipment Simplified. New York, NY: McGraw-Hill Education; 2014.
6. Geddam L, Sankar J. Anesthesia Breathing System: Physical Principles. 2014 [cited 02/09/2023]. In: Anesthesiology Core Reviews: Part 1 Basic Exam [Internet]. McGraw-Hill, [cited 02/09/2023]. Available from: https://accessanesthesiology.mhmedical.com/content.aspx?bookid=974&sectionid=61586856.
7. Asay D, Sankar J. Anesthesia Breathing Circuits: Components. 2014 [cited 02/09/2023]. In: Anesthesiology Core Review: Part One Basic Exam [Internet]. McGraw-Hill, [cited 02/09/2023]. Available from: https://accessanesthesiology.mhmedical.com/book.aspx?bookID=974.
8. Rose G, McLarny J. Anesthesia Machine Ventilators. In: Rose G, McLarny J, editors. Anesthesia Equipment Simplified: McGraw Hill; 2023.

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FCA REFRESHER COURSE

Porphyria

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Introduction

The porphyrias are a group of inherited metabolic disorders caused by altered activities of enzymes within the heme biosynthetic pathway. Altered enzyme activity is mainly due to gene mutation or acquired inhibition of the enzyme. Porphyrias are rare and can be challenging to diagnose since symptoms are nonspecific. Furthermore, they present special anaesthetic challenges perioperatively, especially the gastrointestinal and neurological presentations of acute porphyric crisis. To meet these challenges, this review outlines porphyria pathophysiology, classifications, presentation, management, and the implications of these disorders to the anaesthetist.

Pathophysiology

The heme is metalloporphyrins made from a pyrrole ring and iron ion. It has multiple functions in the body: it is an oxygen and carbon dioxide transporter, it is part of the electron transport chain, and it is a cofactor of several enzymes. Normal heme biosynthesis is made in all tissues but predominantly occurs in the liver and bone marrow. The bone marrow accounts for approximately 80%, whereas the liver produces 20% of overall heme synthesis.[1]

The first step in heme synthesis is the rate-limiting step whereby succinyl-coenzyme A and glycine condense to form δ-aminolevulinic acid (ALA), catalysed by the ALA synthase (ALAS) enzyme found in the mitochondria (Figure 1). The ALAS requires pyridoxal-5'-phosphate (a derivative of vitamin B6) as a cofactor. It occurs in two isoforms that are coded by different genes (ALAS1 and ALAS2).[2] The gene for ALAS1 is found on Chromosome 3 and the enzyme is ubiquitous in all tissues. The ALAS2 is erythroid-specific and is produced by bone marrow erythroblasts. The gene for ALAS2 is located on Chromosome X and its mutations cause sex-linked sideroblastic anaemia or X-linked protoporphyria.

The ALAS is significantly lower than other enzymes in the pathway and varies in expression. Physiologically, heme has a negative feedback loop effect on ALAS activity, limiting the formation of porphyrinogens.[4] Subsequently, the suppression is defective on porphyrias, causing increased enzyme activity. An ALAS is implicated as a toxic molecule, especially to the neurons, and its

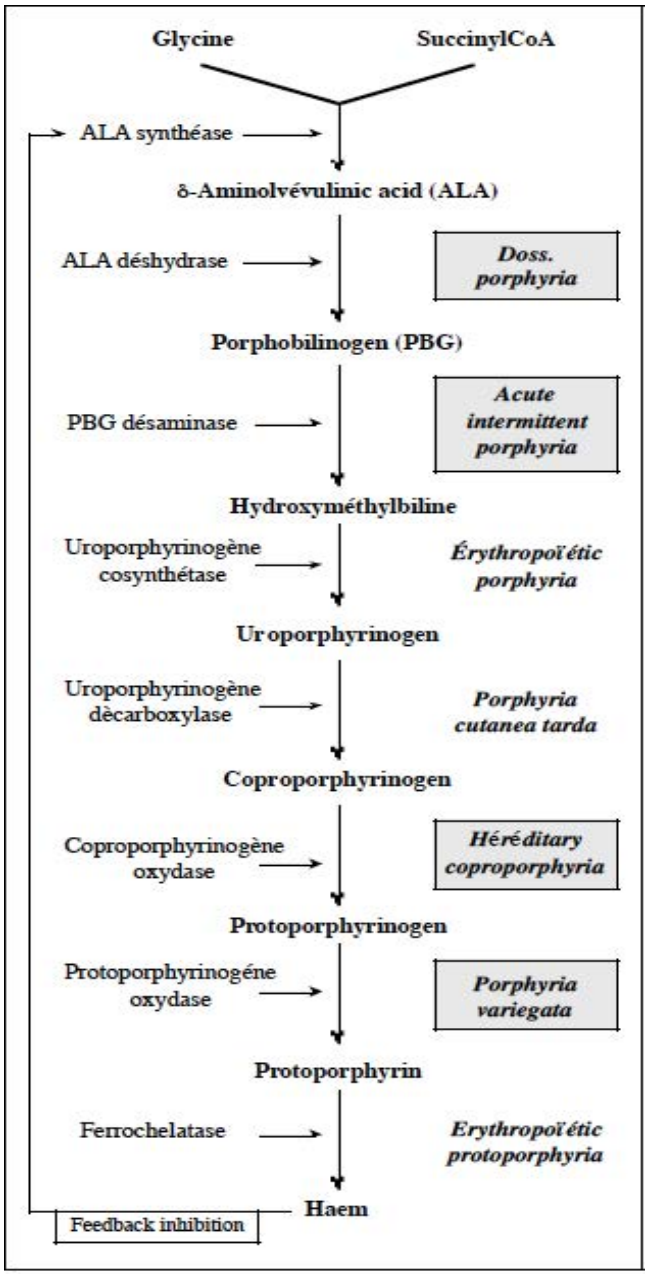

Figure 1: Heme biosynthetic pathway

accumulation is the proposed cause of symptoms in porphyria. The precise mechanism for neuropathy in porphyria is unknown and is a subject of debate. Two hypotheses have been proposed. The one mostly held states that ALA is neurotoxic and causes direct damage to autonomic ganglia, anterior horns of the spinal cord, and peripheral nerves. The second hypothesis suggests that a diminished intraneuronal heme level is responsible for neuropathy.

The first and last three enzymes are mitochondrial, while the other four are in the cytoplasm. All the genes that code these enzymes are in the cellular genome and inheritance of the porphyrias follows Mendelian genetic transmission rather than the mitochondrial.[3]

Therefore, the expressions of porphyria are due to increased ALAS activity, increased porphyrin (organic cyclical compounds found in heme) accumulation in the tissues, or decreased heme production.[5] The increased ALAS activity results in increased levels of heme precursors proximal to the site of the specific enzyme deficiency. These precursors are colourless porphyrinogens that can accumulate in the epidermal skin layers and cause cutaneous photosensitivity.[5]

Epidemiology

The prevalence of acute porphyrias in Europe is estimated to be 1–2 in 100 000, with acute intermittent porphyria (AIP) being the most common.[6] AIP is known as Swedish porphyria since the incidence is estimated to be 1 in 10 000 in Northern Sweden, while variegate porphyria (VP) is known as South African porphyria.[7] VP is common among the Afrikaner community and the prevalence is estimated at 1 in 250 to 1 in 500.[8] ALA dehydratase deficiency is very rare with less than 10 cases reported since 1979.[9] The actual incidence is challenging to assess as most patients remain asymptomatic. This is specifically the case with hereditary coproporphyria (HCP) where more than half the affected patients can be symptom-free.

Classification and presentation of porphyrias

Anaesthetists can be involved in the care of patients with porphyria during acute crisis, surgery, and pain management.[10]

The porphyrias may be classified according to three characteristics:

1. The site of abnormal porphyrin production (hepatic vs. erythropoietic) (Table I)
2. Acute or non-acute presentation
3. The pattern of enzyme deficiency in heme production

This classification reflects the pathophysiology and is useful for the anaesthetist since the acute forms of porphyrias may cause life-threatening reactions to drugs. The acute attacks are characterised by severe abdominal pain, autonomic instability, electrolyte disturbances, and neuropsychiatric manifestations. Neuromuscular weakness, quadriparesis, and respiratory failure is the most severe form of neuropathic dysfunction that can occur; however, seizures may also occur during the acute attack. The abdominal pain is thought to be due to autonomic neuropathy since it is resolved with ganglionic block, though a block is rarely used as the treatment. Also, abdominal pain is severe with characteristic features of alternating areas of spastic and relaxed bowel and is associated with vomiting and diarrhoea. Clinically, the abdominal examination is mostly normal and disproportionate to the pain.

Table I: Classification of porphyrias (Moore at el.[11])

Hepatic
1. *Hepatic acute porphyrias*
a. Acute intermittent porphyria (AIP)
b. Hereditary coproporphyria (HCP)
c. Variegate porphyria (VP)
d. ALA dehydrate deficiency porphyria
2. *Hepatic non-acute porphyria*
a. Porphyria cutanea tarda (PCT)
i. Familial
ii. Acquired
b. Hepatoerythropoietic porphyria (HEP)
Erythropoietic
1. *Erythropoietic porphyria*
a. Uroporphyria
b. Protoporphyria

Dehydration and abnormalities of sodium, potassium, and magnesium can be severe and require adequate management during attacks. Lastly, cardiovascular instability such as tachycardia and hypertension occur particularly with AIP.

Diagnosis

The diagnosis requires a high index of suspicion because the patients are asymptomatic between attacks. A positive family history must raise suspicion and must be followed with laboratory investigation. The urinary and faecal assay of ALA, porphobilinogen (PBG), and porphyrins are used to make a diagnosis. During the latent phase the ALA, PBG, and porphyrins are normal in VP, while for AIP they are raised in both the latent and acute phases. The VP is mainly characterised by increased ALA, PBG, and porphyrins during the acute phase. Genetic testing is preferred in families with a positive family history of porphyria, and it is the most certain diagnostic procedure.[12]

Acute porphyric crisis

Acute attacks occur in only four types of porphyria: AIP, HCP, VP, and plumboporphyria (PLP).[13] Acute porphyrias have the potential to develop crisis, which can be generally triggered by fasting, dehydration, infection, drugs, and alcohol. Acute crises are more common in females than males and present during the third and fourth decades of life. The porphyria crisis can be challenging to identify since the signs and symptoms can be like other conditions such as endometriosis and pelvic inflammatory disease in females (Table II). Tachycardia is frequently a marker of disease state progression; as the heart rate increases the patient's condition generally deteriorates and the opposite is also true.

Table II: Symptoms and signs of acute crisis

Symptoms and signs	Clinical features
Gastrointestinal	Recurrent, severe, poorly localised abdominal pain. Associated with nausea and vomiting. Constipation and gastroparesis are secondary to autonomic dysfunction. Electrolyte disturbance, such as low sodium and magnesium.
Cardiovascular	Tachycardia, atrial fibrillation, hypertension, and postural hypotension.
Central nervous system	Weakness that is proximal more than distal and affects upper limbs more than lower limbs. May progress to respiratory paralysis and bulbar paresis. Seizures due to hyponatraemia. Pain in the back and thigh. Sensory neuropathy over the truck. Mental changes like confusion, mood changes, and psychosis.

The acute attack initiated by the drugs may occur during anaesthesia or perioperatively. Furthermore, drugs can trigger porphyria through four mechanisms:[14] induction of ALAS transcription, interfering with the negative feedback control of ALAS by heme, interfering directly with the heme synthetic pathway, and induction of cytochrome P450 causing high demand for heme. The identification of the drugs most likely to be a porphyric trigger can be difficult, hence the porphyria unit at the University of Cape Town, South Africa, maintains a database of drug safety. The centre can be contacted at www.porphyria.uct.ac.za. Internationally, multiple databases exist, such as the American Porphyria Foundation (www.porphyriafondation.org) and the European Porphyria Centre (www.drugs-pophyria.org).

Treatment

The management of porphyria consists of general, symptomatic/supportive, and targeted treatment. A general measure starts with the identification and elimination of the provoking drugs, hydration, and correction of the electrolytes, specifically hyponatraemia and hypomagnesaemia. The symptomatic treatment depends on the existing symptoms, which differ in each attack. Analgesia such as paracetamol and opioids are safe for pain relief.[15] Cardiovascular symptoms are successfully managed with beta blockers, such as propranolol. The use of diazepam for convulsions is contraindicated because it can induce a crisis. Convulsions are treated with clonazepam and magnesium sulfate, which may be less potent. Nausea responds well to prochlorperazine, ondansetron, and cyclizine; however, metoclopramide must be avoided. The 5% or 10% glucose solution is recommended since carbohydrates decrease ALAS activity.

The targeted treatment in the form of heme supplementation is indicated when there is neuropathy. The intravenous heme solutions are available in two forms, haematin and hemin (heme arginate), which are shown to cause fewer side effects.[16] It is given in a dose of 3 mg/kg, dissolved in 100 ml 0.9% sodium chloride, slowly for four days through a central line. Frequent heme infusions can cause chronic hepatic inflammation due to iron overload. Recently, the Food and Drug Administration (FDA) approved givosiran, a small interfering ribonucleic acid (siRNA) antagonist of ALAS, which is expected to prolong asymptomatic states and delay crises.[17]

Anaesthetic management

Anaesthetic management depends on the current condition of the patient; is the patient in remission or presenting with acute attacks? A patient in remission can safely undergo whichever type of anaesthesia (general and regional anaesthesia). During acute attacks, general anaesthesia is recommended over regional due to the risk of peripheral neuropathy.

In the preoperative period, attention must be focused on hydration, calorie intake, and the electrolyte status of the patient. The autonomic nervous system and cardiorespiratory function should be assessed. The anxiolytics such as midazolam and lorazepam are well tolerated.[8] Analgesia during acute porphyric crises can be achieved with morphine, fentanyl, sufentanil, and non-opioids like paracetamol, indomethacin, and aspirin are considered safe.

The induction and maintenance agent of choice in porphyria is propofol. Ketamine and etomidate show an impact on porphyria crisis onset in animal models; however, in clinical practice, they are considered safe in therapeutic doses.[18]

Volatile anaesthetics are used for the maintenance of general anaesthesia. Both sevoflurane and desflurane are safe even in prolonged administration. Halothane, nitrous oxide, and isoflurane have not caused adverse effects in porphyric patients; however, enflurane has shown porphyrinogen action and should be avoided.[19]

The muscle relaxants and reversals are well tolerated, and succinylcholine safety has been shown in both clinical practice and laboratory conditions.[20] Atracurium has been safely administered in a patient with AIP. The consensus is that muscle relaxants are safe for short-duration usage, but their safety for prolonged administration needs further analysis.

Conclusion

Porphyria has implications for the anaesthetist and anaesthetic drugs can trigger acute porphyric crises. They are challenging to diagnose, and a high index of suspicion needs to be maintained.

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References

1. Fujita H, Yamamoto M, Yamagami T, Hayashi N, Sassa S. Erythroleukemia differentiation. Distinctive responses of the erythroid-specific and

the nonspecific delta-aminolevulinate synthase mRNA. J Biol Chem. 1991;266(26):17494-502. https://doi.org/10.1016/S0021-9258(19)47399-7.
2. Cox TC, Bawden MJ, Martin A, May BK. Human erythroid 5-aminolevulinate synthase: promoter analysis and identification of an iron-responsive element in the mRNA. EMBO J. 1991;10(7):1891-902. https://doi.org/10.1002/j.1460-2075.1991.tb07715.x.
3. Riga JC, Blanloeil Y. Anaesthesia and porphyria. Minerva Anestesiol. 2002;68(5):326-31.
4. Phillips JD. Heme biosynthesis and the porphyrias. Mol Genet Metab. 2019;128(3):164-77. https://doi.org/10.1016/j.ymgme.2019.04.008.
5. Jensen NF, Fiddler DS, Striepe V. Anesthetic considerations in porphyrias. Anesth Analg. 1995;80(3):591-9. https://doi.org/10.1097/00000539-199503000-00028.
6. Wilson-Baig N, Badminton M, Schulenburg-Brand D. Acute hepatic porphyria and anaesthesia: a practical approach to the prevention and management of acute neurovisceral attacks. BJA Educ. 2021;21(2):66-74. https://doi.org/10.1016/j.bjae.2020.09.005.
7. Milner A, Welch E. Applied pharmacology in anaesthesiology and critical care. 1st ed. Centurion: Medpharm Publications; 2012.
8. James MF, Hift RJ. Porphyrias. Br J Anaesth. 2000;85(1):143-53. https://doi.org/10.1093/bja/85.1.143.
9. porphyriafoundation.org [Internet]. A safe/unsafe drug database. American Porphyria Foundation; 2023. Available from: https://porphyriafoundation.org/for-healthcare-professionals/drug-safety/. Accessed 23 September 2023.
10. Findley H, Philips C, Cole D, Nair A. Porphyrias: implications for anaesthesia, critical care, and pain medicine. BJA Educ. 2012;12(3):128-33. https://doi.org/10.1093/bjaceaccp/mks009.
11. Moore MR, McColl KEL, Remington C, Goldberg A. Disorders of porphyrin metabolism. New York: Plenum Medical Book Company; 1987. https://doi.org/10.1007/978-1-4684-1277-2.
12. Anderson KE, Bloomer JR, Bonkovsky HL, et al. Recommendations for the diagnosis and treatment of the acute porphyrias. Ann Intern Med. 2005;142(6):439-50. https://doi.org/10.7326/0003-4819-142-6-200503150-00010.
13. Ramanujam V-MS, Anderson KE. Porphyria diagnostics-part 1: a brief overview of the porphyrias. Curr Protoc Hum Genet. 2015;86(1):17.20.1-26. https://doi.org/10.1002/0471142905.hg1720s86.
14. Iohom G, Fitzgerald D, Cunningham AJ. Principles of pharmacogenetics - implications for the anaesthetist. Br J Anaesth. 2004;93(3):440-50. https://doi.org/10.1093/bja/aeh200.
15. Cargenas JL, Guerrero C. Acute intermittent porphyria: general aspects with focus on pain. Curr Med Res Opin. 2018;34(7):1309-15. https://doi.org/10.1080/03007995.2018.1435521.
16. Green D, Ts'ao CH. Hematin: effects on hemostasis. J Lab Clin Med. 1900;115(2):144-7.
17. Syed YY. Givosiran: a review in acute hepatic porphyria. Drugs. 2021;81(7):841-8. https://doi.org/10.1007/s40265-021-01511-3.
18. Famewo CE. Induction of anaesthesia with etomidate in a patient with acute intermittent porphyria. Can Anaesth Soc J. 1985;32(2):171-3. https://doi.org/10.1007/BF03010045.
19. Randjelovic M, Stojanovic M, Radeka J, Vasilijic M, Jankovic R. Anesthetic implications in porphyrias. Front Anesthesiol. 2023;2:1149949. https://doi.org/10.3389/fanes.2023.1149949.
20. Blekkenhorst GH, Cook ES, Eales L. Drug safety in porphyria. Lancet. 1980;1(8182):1367. https://doi.org/10.1016/S0140-6736(80)92511-8.

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FCA REFRESHER COURSE

Illicit drugs and anaesthesia

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Introduction

About 13.3% of South Africans meet the criteria to be diagnosed with a substance use disorder (SUD) according to the United Nations Office's Drugs and Crime World Drug Report of 2022.[1] The international prevalence of SUD is around 5.5% according to the World Health Organization (WHO). Compared to the rest of the world, this indicates that South Africa's substance use problem is nearly two and a half times larger.[2]

The understanding of addiction has undergone recent changes. SUD is now recognised as a medical disease and is no longer considered merely a symptom of poor self-control or a lack of moral fibre. Removing the stigma of addiction has improved both patient access to rehabilitation and rehabilitation success rates. Much of this shift has come about because of the opioid use disorder (OUD) epidemic in the United States, which has progressively worsened since 2017.[3,4] If one considers that the prevalence of asthma and diabetes mellitus in Africa both are around 12%, then the scale of the SUD epidemic can be appreciated.[5]

After nicotine, alcohol is the most used substance in South Africa. Following these, the list of commonly used substances in South Africa includes cannabis, methaqualone (Mandrax), 3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy), cocaine, methamphetamine (crystal meth/Tik), and heroin.[6] Newer "designer drugs" are constantly being added to the menu of options. Because nicotine and alcohol are not illicit substances, they will not be discussed here.

Classification

It is clinically useful to classify substances as stimulants, depressants, and hallucinogens. Tables I–XI below summarise these and other substances' actions, pharmacokinetics, chemical structure, pharmacodynamics, and adverse effects.

Stimulants

Stimulants usually increase the release or block the reuptake of catecholamines.[7]

Table I: Cocaine[7–12]

Action	Dual mechanism (local anaesthetic and a reuptake inhibitor). Ester local anaesthetic. Presynaptic reuptake inhibitors of adrenaline, noradrenaline, dopamine, and serotonin. Also facilitates catecholamine release.
Pharmacokinetics	Administration: Inhaled or intravenous. Absorption: Bioavailability 30–40% orally and 80–90% inhaled. Metabolism: Plasma and liver cholinesterase. Excretion: Renal. Onset of action: 5–10 minutes inhaled or intravenous. Duration of action: 15 minutes to 1 hour.
Chemical structure	Alkaloid, ester.
Pharmacodynamics	Class 1C Na channel blocker (local anaesthetic effect). Blocks monoamine oxidase inhibitors. Reuptake inhibitor. Central nervous system: Euphoria and excitement.
Adverse effects	Physical and psychological dependence. Nasal septum and soft palate destruction with chronic use could cause airway management challenges.[13] Sympathetic stimulation, anxiety, restlessness, and seizures. Hypertension and myocardial ischemia. Hypotension due to catecholamine depletion after chronic use. Takotsubo cardiomyopathy after chronic use.

Table II: Amphetamines and methylphenidate (Ritalin)[7,9,10,14,15]

Action	Central nervous system stimulant, prescribed for attention-deficit/hyperactivity disorder and narcolepsy. Causes the release of noradrenaline, dopamine and serotonin into the synaptic cleft. Monoamine oxidase inhibitor.
Pharmacokinetics	Administration: Oral, inhaled, or intravenous. Metabolism: CYP2D6 enzyme metabolism. Onset of action: 30 minutes orally, immediately inhaled or intravenous. Duration of action: 4 hours.
Chemical structure	D- and L-isomer. (D-isomer is more potent and more clinically effective).

Pharmacodynamics	Euphoria. Increased energy levels. Increased ability to concentrate (methylphenidate).
Adverse effects	Hypertension, tachycardia, panic attack, and paranoid psychosis. Serotonin syndrome or rhabdomyolysis if used in conjunction with other serotonergic agents or CYP2D6 inhibitor agents. Contraindicated within 14 days of any monoamine oxidase inhibitor use. Prescription methylphenidate should be continued perioperatively to avoid haemodynamic instability from acute withdrawal.[13]

Table III: Methamphetamine/crystal meth (Tik)[7,13]

Action	Catecholamine reuptake inhibitor.
Pharmacokinetics	Administration: Oral, inhaled, or intravenous. Metabolism: Metabolised to amphetamine. Onset of action: 3 hours orally, 5–10 minutes inhaled or intravenous. Duration of action: 6–12 hours.
Chemical structure	Synthesised from ephedrine and pseudoephedrine.
Pharmacodynamics	Euphoria.
Adverse effects	Airway difficulty due to poor oral hygiene ("meth mouth"). Nasal septal necrosis if "snorted". Dysrhythmias, acute coronary syndrome, and aortic dissection. Pulmonary hypertension. Most abused substance in the Western Cape, South Africa.[10]

Table IV: MDMA (Ecstasy)[7,10,13]

Action	Empathogen and entactogen (enhanced social connectivity). Primarily causes serotonin release into the synaptic cleft.
Pharmacokinetics	Administration: Oral. Onset of action: 30–60 minutes orally. Duration of action: About 6 hours.
Chemical structure	Amphetamine.
Pharmacodynamics	Euphoria, sociability, and potential psychedelic effects.
Adverse effects	Serotonin syndrome. Fever, hyponatremia, rhabdomyolysis, renal failure, and liver failure while intoxicated. Low energy ("crash"), low catecholamine levels for days post-use.

Depressants

Table V: Heroin (diacetylmorphine)[10,16,17]

Action	Mu, kappa and delta agonist. Mu1: Analgesia, euphoria, respiratory depression. Mu2: Miosis, ⇓ GIT motility, dependence. Kappa: Analgesia. Twice as potent as morphine.
Pharmacokinetics	Administration: Oral, inhaled, intravenous, or subcutaneous. Absorption: Orally absorbed and then deacetylated to morphine. Metabolism: In central nervous system to monoacetylmorphine; peripherally to 6-monoacetylmorphine; metabolised in plasma, liver, and other tissues. Excretion: 90% renally cleared. Onset of action: 10-20 minutes orally, 3 minutes inhaled, 1 minute intravenous, 5 minutes subcutaneous. Duration of action: Several hours.
Chemical structure	Diacetylmorphine, a semisynthetic derivative of morphine.
Pharmacodynamics	Analgesia, sedation, and respiratory depression.
Adverse effects	Physical dependence. Narrow therapeutic index for respiratory depression. Opioid-induced hyperalgesia complicates analgesia. Withdrawal can present within 6–18 hours after the last dose. Withdrawal will require oral or intravenous opioids. Agonist-antagonist agents such as nalbuphine or antagonists such as naloxone must be avoided to prevent withdrawal.[13]

Table VI: Oxycodone[18]

Action	Mu, kappa and delta agonist. Oxycodone: Morphine dose ratio 1:1.5–2.
Pharmacokinetics	Administration: Oral or inhaled. Metabolism: In the liver by CYP3A4 & CYP2D6 to noroxycodone and oxymorphone. Excretion: Metabolites are excreted renally. Onset of action: 10–30 minutes orally, 2-5 minutes inhaled. Duration of action: 3–6 hours.
Chemical structure	Semisynthetic opioid.
Pharmacodynamics	Analgesia, sedation, and respiratory depression.
Adverse effects	Physical dependence. Nasal septum and soft palate necrosis in patients who "snort" crushed tablets.

Table VII: Methaqualone (Mandrax)[10]

Action	Gamma-aminobutyric acid stimulant. Barbiturate-like central nervous system depressant.
Pharmacokinetics	Administration: Oral. Excretion: Renal. Onset of action: 30 minutes. Duration of action: 4–8 hours.
Pharmacodynamics	Euphoria, anxiolysis, and sedation.
Adverse effects	Withdrawal: 12–24 hours after the last dose.

Hallucinogens

Table VIII: Phencyclidine (PCP, "angel dust")[9,19,20]

Action	N-methyl-D-aspartate antagonist. Dopamine agonist, partial adrenergic agonist, and serotonin antagonist.

Pharmacokinetics	Administration: Oral or inhaled. Metabolism: Hepatic. Excretion: Renal. Onset of action: 30–60 minutes orally, 2–5 minutes inhaled. Duration of action: 4–8 hours.
Chemical structure	Precursor of ketamine.
Pharmacodynamics	Causes a dissociative state.
Adverse effects	Tachycardia, hypertension, psychosis, nystagmus, cerebral haemorrhage, and a depressed level of consciousness.

Table IX: Lysergic acid diethylamide (LSD)[9,10,13,21]

Action	Hallucinogen.
Pharmacokinetics	Administration: Oral. Onset of action: 30–60 minutes. Duration of action: 6–10 hours.
Chemical structure	Similar to serotonin. R- (more potent) and S-isomers.
Pharmacodynamics	Direct stimulation of serotonin receptors (5HT2A and 5HT2AR).
Adverse effects	Significant variation in effects may cause anxiety, fear, panic and hallucinations ("bad trip"). Psychological dependence and antisocial behaviour.

Other agents

Table X: Marijuana[9,13,22,23]

Action	Muscarinic inhibitor. (No longer illicit for private consumption at home).
Pharmacokinetics	Administration: Usually smoked or ingested orally (edibles). Metabolism: Hepatic (CYP enzymes). Onset of action: Orally 30 minutes to 2 hours, inhaled 3–10 minutes. Duration of action: Oral for up to 24 hours, inhaled 1–3 hours.
Chemical structure	Delta-9-tetrahydrocannabinol.
Pharmacodynamics	Euphoria, sedation and drunken feeling.
Adverse effects	Chronic cough with chronic smoking (less compared to cigarette smoking). Enhances the effect of stimulants or depressants if used in combination.

Table XI: Nyaope[24,25]

Action	Similar to marijuana, heroin and other additives.
Pharmacokinetics	Administration: Intravenous, smoked, often with marijuana.
Chemical structure	Mostly heroin, plus any of several additives such as Zidovudine (ARV), codeine, opiates, caffeine, and amphetamines.
Pharmacodynamics	Euphoria.
Adverse effects	Highly addictive (heroin). Respiratory depression. Severe withdrawal with abdominal pain, and seizures.

Anaesthetic implications

While a SUD patient may present for surgery having only used one substance, it is not uncommon for these patients to have been exposed to a cocktail of stimulants and depressants simultaneously, complicating the clinical picture. Up to 83% of SUD patients who present for surgery have used at least two agents, commonly alongside alcohol.[26]

Among substances encountered by the anaesthesiologist, OUD is particularly in the spotlight in America.[4] While there is a strident call to improve opioid stewardship in the primary care setting, it is recognised that the perioperative prescription of opioids has little effect on long-term addiction.[27]

When patients with SUD, including OUD, present for elective surgery, a multidisciplinary perioperative analgesia plan, with patient input, is recommended.[4,7]

Acute intoxication

Wherever possible, the patient who presents acutely intoxicated should be postponed until the substance has been cleared to avoid haemodynamic instability.[13] The management of acute toxicity is largely supportive. Any additional agents required will depend on the substance involved and the clinical picture.

Stimulant intoxication will present with a sympathomimetic clinical picture, with the differential diagnosis of thyrotoxicosis, malignant hyperthermia, neurolept malignant syndrome, and opioid withdrawal.[7] In the case of toxicity from stimulants, acute central nervous system and cardiovascular system toxicity can be managed with a variety of agents. Dexmedetomidine (alpha-2 agonist) has recently gained popularity for this role.[28] Other commonly used agents include benzodiazepines, direct-acting vasodilators, calcium channel blockers, and mixed alpha and beta antagonists.[7] The use of selective beta blockers, which would leave the patient exposed to unopposed alpha stimulation, is controversial and generally not recommended.[7] The successful use of intravenous lipid emulsion to counteract the toxicity of lipid-soluble agents, such as psychotropic agents and cocaine, is also described.[11,28]

In the case of a depressant substance toxicity, the management is again supportive, (especially in terms of respiratory depression) with the additional options of naloxone and flumazenil as antidotes for opioids and benzodiazepines, respectively.[26]

Acute withdrawal

The clinical picture will depend on whether the patient is suffering withdrawal from a stimulant or a depressant agent. The patient may present with a spectrum from mild tremors, fever, and electrolyte derangement to haemodynamic instability, altered consciousness, and seizures. Psychostimulant agent withdrawal may present with depression, a decreased consciousness level, lethargy, and haemodynamic depression or potentially with anxiety, agitation, and psychosis.[7]

Dexmedetomidine and benzodiazepines form the mainstay of the management of withdrawal from depressant agents such as alcohol or opioids in conjunction with further supportive management, such as inotropic support where required.[13,29]

Chronic SUD

All patients presenting for surgery, including the SUD patient, must be assured that they will be offered adequate and appropriate analgesia. The 2022 Centers for Disease Control and Prevention (CDC) clinical practice guideline recommends the maximised use of multimodal analgesic agents and regional techniques to reduce opiate requirements as much as possible in chronic SUD patients. However, where necessary, it is not recommended to withhold opiates.[30,31] The use of opioids in these patients should be at the lowest effective dose and for the shortest required duration. These patients may exhibit hyperalgesia and it may be difficult to control their pain with opioids alone. Hence the recommendation is to use multimodal analgesia, including regional techniques, as far as possible. Where opioids are used, the more potent, shorter-acting agents such as sufentanil and fentanyl are recommended.[4] If opioids are used for longer than a few days, their dose should be tapered and not stopped abruptly.[31]

A patient being rehabilitated for OUD may present for surgery on methadone (Table XII) or buprenorphine (Table XIII). It is recommended that these are continued through the perioperative period. The SUD patient may also present additional challenges, such as difficult intravenous access, a difficult airway, an altered level of consciousness, and a stormy haemodynamic perioperative course.[13]

The chronic cocaine SUD patient may present with catecholamine depletion and fewer postsynaptic receptors, which require the use of higher doses of direct-acting vasopressors or inotropes, as indirect-acting agents will not be able to facilitate the release of endogenous catecholamines.[7,11] Refractory hypotension in these patients may require the use of vasopressin.[7]

Medications for OUD

Table XII: Methadone[4,9,13,32]

Action	Mu agonist and N-methyl-D-aspartate receptor antagonist. Also, serotonin and noradrenaline reuptake inhibitors. Prescribed for chronic opioid rehabilitation in patients with OUD and for chronic pain patients.
Pharmacokinetics	Administration: Oral, intravenous, or subcutaneous. Metabolism: Hepatic (CYP enzymes). Excretion: Stool and urine. Onset of action: 60 minutes. Duration of action: 6–8 hours (t1/2 8–59 hours).
Chemical structure	Synthetic opioid.
Pharmacodynamics	Analgesia.
Adverse effects	Withdrawal begins 24–48 hours after the last dose. Prolonged QT and possible torsade de pointes. Respiratory depression in overdose, may be lethal in combination with other sedative/depressant agents.

Table XIII: Buprenorphine[4]

Action	Opioid agonist-antagonist (partial mu agonist, kappa antagonist).
Pharmacokinetics	Administration: Oral, sublingual, intravenous, or transdermal. Onset of action: 30–60 minutes. Duration of action: 6–12 hours.
Chemical structure	Morphinan alkaloid.
Pharmacodynamics	Potent analgesia with less respiratory depression and euphoria.
Adverse effects	Nausea, vomiting, drowsiness, orthostatic hypotension, and urinary retention.

Conclusion

Managing a SUD patient in the perioperative space requires an understanding of the potential effects and drug interactions of the substance used. It is a valuable contact time for postoperative referral for counselling, but not the time for rehabilitation. Furthermore, inadequately managing a patient's pain may do more harm and potentially push a recovering SUD patient to relapse.[31]

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References

1. World drug day 2023. Badisa; 2023. Available from: https://badisa.org.za/2023/06/22/world-drug-day-2023/#. Accessed 2 September 2023.
2. World Health Organization. Drugs (psychoactive). Available from: https://www.who.int/health-topics/drugs-psychoactive#tab=tab_2. Accessed 2 September 2023.
3. Nathan N. At the frontline of opioid use disorder. Anesth Analg. 2023;137(3):469. https://doi.org/10.1213/ANE.0000000000006638.
4. Barreveld AM, Mendelson A, Deiling B, et al. Caring for our patients with opioid use disorder in the perioperative period: a guide for the anesthesiologist. Anesth Analg. 2023;137(3):488-507. https://doi.org/10.1213/ANE.0000000000006280.
5. Sifunda S, Mbewu AD, Mabaso M, et al. Prevalence and psychosocial correlates of diabetes mellitus in South Africa: results from the South African National Health and Nutrition Examination Survey (SANHANES-1). Int J Environ Res Public Health. 2023;20(10):5798. https://doi.org/10.3390/ijerph20105798.
6. News24.com [Internet]. 9 most common street drugs. News24; 2013. Available from: http://www.health24.com/Mental-Health/Alcohol/Drugs-special-report-20120721. Accessed 2 September 2023.
7. Emerick TD, Martin TJ, Ririe DG. Perioperative considerations for patients exposed to psychostimulants. Anesth Analg. 2023;137(3):474-87. https://doi.org/10.1213/ANE.0000000000006303.
8. Richards JR, Laurin EG. Cocaine [Internet]. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430769/. Accessed 2 September 2023.
9. Vadivelu N, Mitra S, Kaye AD, Urman RD. Perioperative analgesia and challenges in the drug-addicted and drug-dependent patient. Best Pract Res Clin Anaesthesiol. 2014;28(1):91-101. https://doi.org/10.1016/j.bpa.2014.02.003.
10. Balkisson MA. Drugs of abuse and the implications for anaesthesia and critical care. University of KwaZulu-Natal. 2020;1-17. Available from: https://q8c7r2f7.stackpathcdn.com/wp-content/uploads/2020/07/03-July-2020-Drugs-of-Abuse-and-the-implications-for-Anaesthesia-and-Critical-Care-M-Balkisson.pdf. Accessed 2 September 2023.
11. Jakkala-Saibaba R, Morgan PG, Morton GL. Treatment of cocaine overdose with lipid emulsion. Anaesthesia. 2011;66(12):1168-70. https://doi.org/10.1111/j.1365-2044.2011.06895.x.
12. O'Donnell K, Boyle S, Abdulrahman S, O'Leary E. Unexpected intraoperative hypotension in a chronic cocaine user. Anaesth Rep. 2022;10(2):e12177. https://doi.org/10.1002/anr3.12177.
13. Moran S, Isa J, Steinemann S. Perioperative management in the patient with substance abuse. Surg Clin North Am. 2015;95(2):417-28. https://doi.org/10.1016/j.suc.2014.11.001.
14. Martin D, Le JK. Amphetamine [Internet]. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556103/. Accessed 2 September 2023.

15. Faraone SV. The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehav Rev. 2018;87:255-70. https://doi.org/10.1016/j.neubiorev.2018.02.001.
16. Huecker MR, Koutsothanasis GA, Abbasy MSU, Marraffa J. Heroin [Internet]. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441876/?report. Accessed 2 September 2023.
17. Milella MS, D'Ottavio G, De Pirro S, et al. Heroin and its metabolites: relevance to heroin use disorder. Transl Psychiatry. 2023;13(1):120. https://doi.org/10.1038/s41398-023-02406-5.
18. Sadiq NM, Dice TJ, Mead T. Oxycodone [Internet]. StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482226/. Accessed 2 September 2023.
19. Morris BJ, Cochran SM, Pratt JA. PCP: from pharmacology to modelling schizophrenia. Curr Opin Pharmacol. 2005;5(1):101-6. https://doi.org/10.1016/j.coph.2004.08.008.
20. U.S. Department of Justice Drug Enforcement Administration. Phencyclidine. Diversion Control Division; 2023. Available from: https://www.deadiversion.usdoj.gov/drug_chem_info/pcp.pdf. Accessed 2 September 2023.
21. Hwang KAJ, Saadabadi A. Lysergic acid diethylamide (LSD). StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482407/?report. Accessed 2 September 2023.
22. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. Br J Clin Pharmacol. 2018;84(11):2477-82. https://doi.org/10.1111/bcp.13710.
23. Americanaddictioncenters.org [Internet]. Marijuana edibles: risks, side effects & dangers. American Addiction Centers; 2022. Available from: https://americanaddictioncenters.org/marijuana-rehab/risks-of-edibles. Accessed 2 September 2023.
24. Khine AA, Mokwena KE, Huma M, Fernandes L. Identifying the composition of street drug Nyaope using two different mass spectrometer methods. Afr J Drug Alcohol Stud. 2015;14(1):49-56.
25. Strauss L. Nyaope and anaesthesia. South Afr J Anaesth Analg. 2022;28(5 Suppl 1):S150-5.
26. Hall AP, Henry JA. Illicit drugs and surgery. Int J Surg. 2007;5(5):365-70. https://doi.org/10.1016/j.ijsu.2006.06.006.
27. McIsaac DI, Ladha KS. Postoperative opioid prescribing: finding the balance. Anesthesiology. 2022;137(2):131-3. https://doi.org/10.1097/ALN.0000000000004297
28. Wong GTC, Irwin MG. Poisoning with illicit substances: toxicology for the anaesthetist. Anaesthesia. 2013;68(Suppl 1):117-24. https://doi.org/10.1111/anae.12053.
29. Ruiz FJ, Warner NS, Acampora G, Coleman JR, Kohan L. Substance use disorder: basic overview for the anesthesiologist. Anesth Analg. 2023;137(3):508-20. https://doi.org/10.1213/ANE.0000000000006281.
30. Lerchl-Wanie G, Angster R. [Perioperative analgesia for opioid tolerant patients]. Anaesthesist. 2010;59(7):657-72. German. https://doi.org/10.1007/s00101-010-1757-z.
31. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. Prescribing opioids for pain - the new CDC clinical practice guideline. N Engl J Med. 2022;387(22):2011-3. https://doi.org/10.1056/NEJMp2211040.
32. Sunilkumar MM, Lockman K. Practical pharmacology of methadone: a long-acting opioid. Indian J Palliat Care. 2018;24(Suppl 1):S10-4. https://doi.org/10.4103/IJPC.IJPC_180_17.

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FCA REFRESHER COURSE

Antiplatelet agents

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Introduction

Platelets play an important role in haemostasis after tissue injury. However, due to their inherent function, platelets are also involved in atherosclerotic thrombo-occlusive diseases of the cardiovascular and cerebrovascular systems.[1,2] The formation of a thrombus is currently best explained by a cell-based model, comprising three processes of coagulation-initiation, amplification, and propagation.[3]

By studying platelets' mechanisms of adhesion, activation, and amplification, the ability to develop treatment, management, and prevention of acute coronary syndromes, stent thrombosis, and stroke in individuals at risk, improves.[4] Knowledge of antiplatelet drugs has substantial value in the perioperative setting.[5]

Platelet physiology

The physiology and function of platelets extend beyond coagulation and the scope of this article. To understand the mechanism of platelet inhibition by antiplatelet medication, the basic physiology of platelet activation is pertinent to grasp (Figure 1).[4]

Platelets circulate in blood in a resting state and do not interact with the vessel wall.[4,6,7] Vascular injury or atherosclerotic plaque rupture exposes the vascular subendothelium to circulating platelets.[1,4,6] The glycoprotein (GP) Ib/IX/V receptor complex on platelets binds to exposed von Willebrand factor, initiating platelet adhesion.[1,6] Subsequently, the thrombogenic collagen present in the subendothelial matrix is bound by platelet GP VI and integrin $\alpha 2\beta 1$ receptors.[1,6]

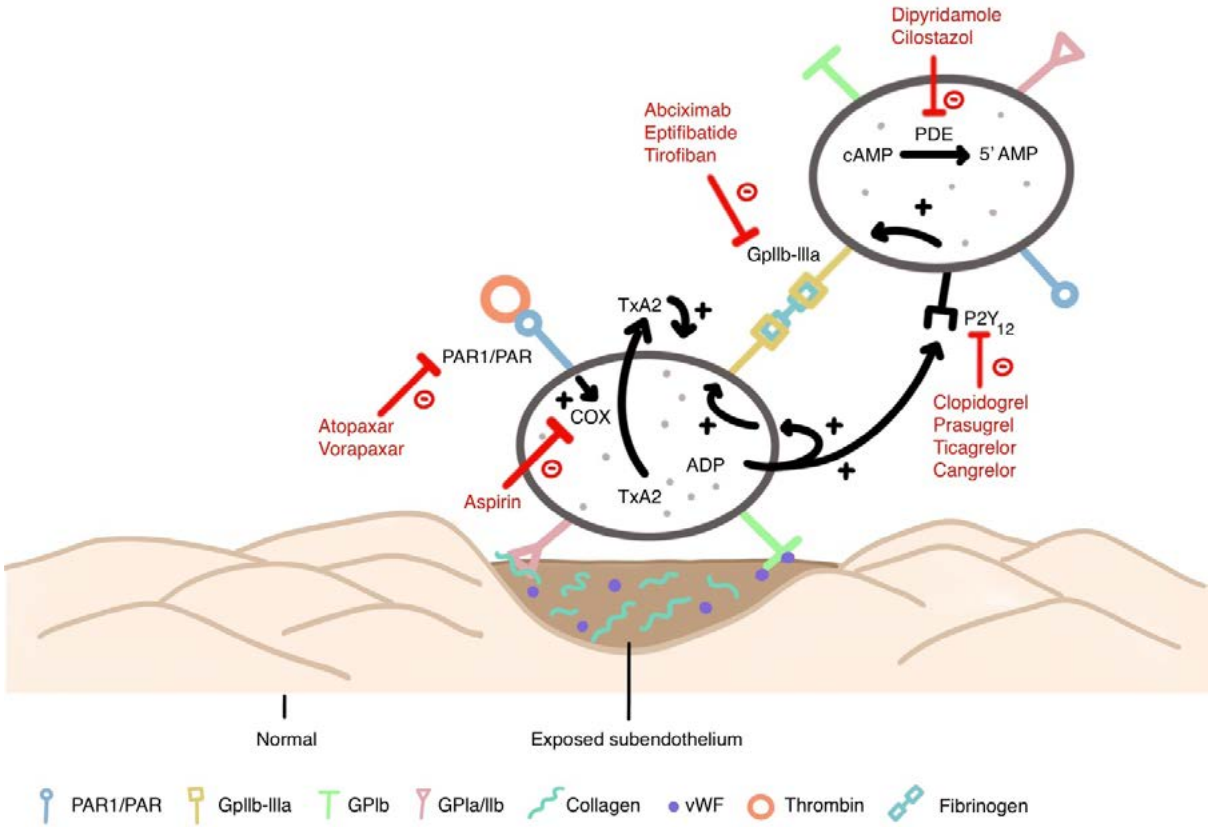

Figure 1: An overview of platelet response to vessel damage and antiplatelet receptor binding sites[1,6,8]

During activation, changes to platelet morphology and mobilisation of intracellular calcium result in the release of adenosine diphosphate (ADP) and thromboxane A2 (TxA2), which maintain platelet activation as well as promote activation of the final common pathway for platelet aggregation via the GP IIb/IIIa receptors.[1,6,7] The P2Y12 receptor on platelets is a critical binding site for ADP to maintain GP IIb/IIIa receptor activation.[1,6]

Stable thrombus formation occurs due to the binding of platelets to each other via activated GP IIb/IIIa receptors to fibrinogen.[1,6,7] Thrombin, P-selectin, and CD40L are agonists in platelet activation that facilitate thrombus formation and adhesion.[1,6] Protease-activated receptors (PARs) undergo proteolytic cleavage by serine protease thrombin, one of the most potent drivers of platelet activation and aggregation.[6] Furthermore, thrombin converts fibrinogen to fibrin, which creates a fibrin and platelet matrix resulting in a stable thrombus.[6]

Drug classes (Table I)

Table I: Antiplatelet drugs classified according to class[8]

Class	Drugs
Cyclooxygenase inhibitors	Aspirin
ADP receptor inhibitors	Clopidogrel, prasugrel, ticlopidine, ticagrelor, cangrelor
Phosphodiesterase inhibitors	Cilostazol
GP IIb/IIIa receptor antagonists	Abciximab, tirofiban, eptifibatide
Adenosine reuptake inhibitors	Dipyridamole
Protease-activated receptor (PAR-1) antagonist	Vorapaxar

Cyclooxygenase inhibitors

Aspirin

Aspirin irreversibly acetylates cyclooxygenase-1 (COX-1) at low doses.[8,9] Inhibition of COX-1 within platelets prevents the synthesis of TxA2.[5] In addition to COX-1, COX-2 is also inhibited by aspirin at higher doses and is responsible for the anti-inflammatory effects.[9,10] Aspirin is rapidly absorbed by the upper gastrointestinal tract, reaches peak plasma concentration in 20–40 minutes, is mostly metabolised by the liver, and has a half-life of 15–30 minutes.[9,10]

The effect of aspirin lasts for the life of the platelets (7–10 days); however, platelet function recovers by 10% per day due to the production of new platelets.[10] Adverse effects commonly include dyspepsia, gastritis, peptic ulcers, and more rarely anaphylaxis.[4,10]

ADP receptor inhibitors

Clopidogrel

Clopidogrel is a prodrug that is metabolised in the liver and is considered a thienopyridine.[3,6,9] Approximately 15% of clopidogrel is metabolised by cytochrome P450 (CYP450) isoenzymes via a two-step process to its active form.[6,9] The remainder of the absorbed drug is converted by hepatic carboxylesterase 1 to an inactive molecule.[6,9] The active metabolite selectively binds the G-coupled P2Y12 receptor irreversibly on platelets preventing the binding of ADP on the receptor.[4,6] The reliance on CYP450 for metabolism predisposes clopidogrel to drug-drug interactions.[6,9] Genetic polymorphisms and drugs that inhibit CYP2C19, such as proton-pump inhibitors, are implicated in the variable response of clopidogrel.[3,6]

The onset of action occurs in a dose-dependent fashion, a loading dose of 300 mg is required to achieve a therapeutic effect in 6–8 hours.[4,10] The effect lasts for the life of the platelets and the offset of action is 5–7 days.[9] Bleeding is a common side effect presenting as epistaxis or gastrointestinal bleeding, as well as dermatological manifestations such as skin rashes and pruritis.[4,10] A rare life-threatening complication is neutropaenia, which occurs more frequently with ticlopidine.[10]

Prasugrel

Prasugrel is a third-generation thienopyridine similar to clopidogrel as a prodrug and its metabolite irreversibly inactivates the P2Y12 receptor.[3,4,9] In contrast to clopidogrel, the active thiolactone metabolite of prasugrel provides a rapid onset of action, more reliable bioavailability, and less drug-drug interactions with CYP450.[6,9] Due to its potent antiplatelet effects, prasugrel is more effective than clopidogrel at preventing thrombosis; however, at an increased risk of serious and fatal bleeding.[10] Prasugrel should be stopped 7–10 days before surgery.[9]

Ticagrelor

Ticagrelor is classified as a cyclopentyltriazolopyrimidine.[6] It is a non-competitive allosteric antagonist with reversible binding for the P2Y12 receptor.[10] As a result of its reversible binding to the ADP receptor, it has a bioavailability of 36% and variable efficacy depending on plasma concentration.[9] Ticagrelor is not a prodrug and does not need to be metabolised to have an effect; however, its metabolite is equally effective at inhibiting the P2Y12 receptor.[4,6] It is metabolised in the liver by CYP450 isoenzymes CYP3A4 and CYP3A5.[3,6,9] Drugs that are metabolised by or inhibit CYP3A4 and CYP3A5 can potentially delay the metabolism of ticagrelor.[4,9] The metabolism of digoxin is affected when administered concurrently with ticagrelor and careful monitoring of digoxin levels should be instituted.[6,9,10]

Ticagrelor reaches maximum plasma concentration within 1.5 hours of administration and has a plasma half-life of seven hours.[9] Offset of action is five days and it should be withheld for seven days before surgery.[9] The side effect profile of ticagrelor is similar to thienopyridines, but there are additional respiratory and adverse cardiac effects of ticagrelor-dyspnoea and bradycardia.[4,6,10]

Cangrelor

Cangrelor, a reversibly binding inhibitor of the P2Y12 receptor, is an adenosine triphosphate analogue that acts directly on the receptor.[6] It is one of the newer antiplatelet drugs administered

by intravenous infusion, has an immediate onset of action, and a plasma half-life of 3–5 minutes.[6,9] The metabolism of cangrelor occurs rapidly in the plasma by plasmatic ectonucleotidases to an inactivated metabolite.[6]

The unique properties of cangrelor make it ideal for procedural therapy as platelet function returns to normal after one hour of stopping the infusion.[6,9] Caution should be taken when administering cangrelor with thienopyridine drugs as their active metabolites are unable to effectively bind the P2Y12 receptor at the same time.[6]

Phosphodiesterase inhibitors

Cilostazol

As a phosphodiesterase-3 inhibitor, cilostazol is primarily a vasodilator indicated for the treatment of claudication.[4,11] It prevents platelet aggregation and encourages vasodilation by preventing the breakdown of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) within platelets and vascular smooth muscle cells.[4,11] Elevated cAMP levels also decrease protein kinase A activity and reduce the release of P-selectin.[11] Cilostazol reaches peak plasma concentration in three hours with an elimination half-life of 11–13 hours.[4,10]

Cilostazol's effect on platelet aggregation is reversible.[11] The side effect profile of cilostazol includes anaemia, thrombocytopenia, and agranulocytosis.[4,10] Cilostazol is contraindicated in congestive heart failure.[10]

GP IIb/IIIa receptor antagonists

Abciximab

Abciximab is the earliest of the GP IIb/IIIa receptor antagonists.[7,10] It is a recombinant monoclonal antibody that binds reversibly on platelets' GP IIb/IIIa receptor.[6,7] Abciximab has the highest affinity for the GP IIb/IIIa receptor amongst the antiplatelet drugs.[9] Platelet binding occurs rapidly after administration, and despite its short plasma half-life of 10–30 minutes, it has a much longer biological effect.[6,9] Platelet function is adequate 48 hours after cessation of intravenous infusion; however, due to its high affinity for the receptor, residual activity of abciximab may be found in the circulation after 15 days.[3,9] The most common side effect of GP IIb/IIIa inhibitors is bleeding.[4,10] Other side effects of abciximab are thrombocytopenia, nausea, and chest pain.[4,10]

Tirofiban

Tirofiban is a synthetic nonpeptide small molecule.[7,10] It is a peptidomimetic analogue of tyrosine and mimics the sequencing arginine-glycine-aspartate (RGD) that reversibly inhibits the GP IIb/IIIa receptor.[6,7,10] The onset of action and efficacy is dose-dependent and platelet inhibition occurs at five minutes, the plasma half-life is two hours, and the return to normal platelet function takes 4–8 hours.[6,9] The metabolism and clearance of tirofiban are affected by renal dysfunction as 65% of the drug is excreted by the kidneys.[3,6] Tirofiban has a faster onset of action relative to abciximab, but less affinity for the GP IIb/IIIa receptor results in a shorter duration of action.[6] Of note, tirofiban is associated with coronary artery dissection.[4]

Eptifibatide

Eptifibatide, like tirofiban, is a reversible synthetic GP IIb/IIIa antagonist. But eptifibatide is a cyclic heptapeptide that is sequenced lysine-glycine-aspartate (KGD), like the integrin antagonist barbourin found in snake venom.[6,7] Eptifibatide has a rapid onset of action and its receptor occupancy and level of platelet inhibition are dose-dependent.[9] It has predominant renal excretion and a plasma half-life of two hours with an offset of action of four hours.[3,6,9]

Adenosine reuptake inhibitors

Dipyridamole

Dipyridamole is both an adenosine reuptake inhibitor as well as a phosphodiesterase-5 inhibitor.[3,4] It prevents the cellular uptake of adenosine, thereby decreasing the platelets' ability to adhere to the vessel wall and it inhibits phosphodiesterase, which in turn leads to increased intracellular cAMP, decreased intracellular calcium, and enhanced effectiveness of prostacyclin.[3,4] Dipyridamole can be administered both orally and intravenously.[4] It is less effective at preventing platelet aggregation than it is at preventing platelet adhesion.[3] It is a potent coronary artery vasodilator but a comparatively weak antiplatelet agent and is often prescribed in combination with aspirin for the prevention of cerebrovascular accidents.[3,4]

PAR-1 antagonist

Vorapaxar

Vorapaxar falls into a relatively new class of antiplatelet drugs that bind to and inhibit the PAR-1 and thrombin receptor activating peptide (TRAP) on platelets.[4,5,10] The PAR-1 is responsible for platelet activation when bound to thrombin.[1] Vorapaxar is a fast-acting, reversible, dose-dependent peptide inhibitor of PAR-1.[6,10] A dose of 5–40 mg of vorapaxar may result in more than 90% reduction of platelet aggregation due to the inhibition of TRAP.[6] Vorapaxar does not affect the coagulation properties of thrombin or interfere with the conversion of fibrinogen to fibrin.[6,10] It has an extended half-life of eight days and is metabolised by CYP3A4 in the liver.[10] Contraindications to vorapaxar include a history of stroke and transient ischaemic attack as administration carries an increased risk of intracranial haemorrhage.[10] Although rare, other side effects associated with vorapaxar are anaemia, skin rashes, and headaches.[4,10]

Conclusion

Antiplatelet agents are useful in the prevention and management of thrombo-occlusive vascular diseases.[8] The ideal antiplatelet agent still does not exist; however, as the understanding of signalling pathways and receptors improves, so does the ability

to create better drugs.[6] Antiplatelet agents under development, such as picotamide, terutroban, and PZ-128 may provide a better alternative to agents currently available.[6]

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References

1. Thijs T, Nuyttens BP, Deckmyn H, Broos K. Platelet physiology and antiplatelet agents. Clin Chem Lab Med. 2010;48(Suppl 1):S3-S13. https://doi.org/10.1515/CCLM.2010.363.
2. Filipescu DC, Stefan MG, Valeanu L, Popescu WM. Perioperative management of antiplatelet therapy in noncardiac surgery. Curr Opin Anaesthesiol. 2020;33(3):454-62. https://doi.org/10.1097/ACO.0000000000000875.
3. Peck T, Harris B. Drugs affecting coagulation. In: Peck T, Harris B. Pharmacology for anaesthesia and intensive care. 5th ed. Cambridge: Cambridge University Press; 2021. p. 331-45. https://doi.org/10.1017/9781108591317.025.
4. Blas JV, Tingen JS, Taylor SM. Antiplatelet agents. In: Perler BA, Sidawy AP, editors. Rutherford's vascular surgery and endovascular therapy. 10th ed. Philadelphia: Elsevier; 2022. p. 540-9.
5. Mahmood H, Siddique I, McKechnie A. Antiplatelet drugs: a review of pharmacology and the perioperative management of patients in oral and maxillofacial surgery. Ann R Coll Surg Engl. 2020;102(1):9-13. https://doi.org/10.1308/rcsann.2019.0154.
6. Kalra K, Franzese CJ, Gesheff MG, et al. Pharmacology of antiplatelet agents. Curr Atheroscler Rep. 2013;15(12):371. https://doi.org/10.1007/s11883-013-0371-3.
7. Hook KM, Bennett JS. Glycoprotein IIb/IIIa antagonists. Handb Exp Pharmacol. 2012;(210):199-223. https://doi.org/10.1007/978-3-642-29423-5_8.
8. Seto AH. Interventional pharmacology. In: Kern MJ, Sorajja P, Lim MJ, editors. The interventional cardiac catheterization handbook. 4th ed. Philadelphia: Elsevier; 2018. p. 109-29. https://doi.org/10.1016/B978-0-323-47671-3.00003-X.
9. Koenig-Oberhuber V, Filipovic M. New antiplatelet drugs and new oral anticoagulants. Br J Anaesth. 2016;117(Suppl 2):ii74-84. https://doi.org/10.1093/bja/aew214.
10. Baber JT, O'Connell JB. Medical management of vascular disease-including pharmacology of drugs used in vascular disease management. In: Moore WS, Lawrence PF, Oderich GS, editors. Moore's vascular and endovascular surgery: a comprehensive review. 9th ed. Philadelphia: Elsevier; 2019. p. 202-15.
11. Kherallah RY, Khawaja M, Olson M, Angiolillo D, Birnbaum Y. Cilostazol: a review of basic mechanisms and clinical uses. Cardiovasc Drugs Ther. 2022;36(4):777-92. https://doi.org/10.1007/s10557-021-07187-x.

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FCA REFRESHER COURSE

Anaesthesia breathing systems

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Anaesthetic breathing systems are used to provide oxygen and anaesthetic gases to a patient and to remove carbon dioxide (CO_2). Anaesthesia breathing systems are complex but important; they keep patients alive. A good understanding of their history and how they work is important for safe anaesthetic practice.

This article discusses the main components of anaesthesia breathing systems and the characteristics of an ideal breathing system. Furthermore, the various classifications of breathing systems are explored, and non-circle systems are compared to traditional circle systems.

Keywords: breathing systems, Mapleson, circle system

Anaesthesia breathing systems

Anaesthetic breathing systems are used to provide oxygen and anaesthetic gases to a patient and to remove CO_2.[2]

These are the main components of breathing systems:

1. Adjustable pressure limiting (APL) valve.
2. Reservoir bag.
3. Inspiratory and expiratory limb breathing tubes.
4. Connectors and adaptors.[1,3]

APL valve

The APL valve allows the anaesthetist to change the pressure within the breathing system. The valve is a one-way spring-loaded valve. When the valve is adjusted to a certain pressure, it allows gas to leak out of the breathing system to maintain the patient's airway pressure. The minimum pressure produced is 1 cmH_2O. A safety feature prevents pressure from exceeding 60 cmH_2O.[3]

Reservoir bag

The reservoir bag is made of antistatic rubber or plastic. Fresh gas flow (FGF) collects in this bag during expiration, reducing the amount of fresh gas required to prevent rebreathing. It can be used to monitor the patient's breathing pattern if they are breathing spontaneously. Sizes range from 0.5 to 2 L in our setting. The reservoir bag helps to limit pressure within the breathing system through the expansion of the bag to reduce pressure (Laplace's law).[1,3]

Inspiratory and expiratory limbs

The inspiratory limb supplies FGF to the patient for inspiration and the expiratory limb carries the gas flow expired by the patient back into the system. The tubing is corrugated for flexibility and increased resistance to kinking. It is usually made from clear plastic and is lightweight and with low resistance. The adult systems are approximately 22 mm and the paediatric systems are 18 mm in diameter.[1,3]

Characteristics of an ideal breathing system[1]

- Simple, safe, and inexpensive.
- Delivers intended inspired gas mixture.
- Allows for spontaneous, controlled, or assisted ventilation of all age groups.
- Efficient and allows for low FGF.
- Able to protect patients from barotrauma.
- Compact, light, and strong.
- Easily removes waste gases.
- Warms and humidifies inspired gases.
- Effectively eliminates CO_2.
- Low resistance means minimal length, maximal internal diameter, and consistent diameter.
- Minimal dead space.

Classification of breathing systems

There are many ways of classifying breathing systems.

1. The old classification:
   - Used the terms open, closed, semi-open, and semi-closed.
   - Described by Dripps (United States of America), Conway (United Kingdom), and others.[1]
   - Definitions vary and are confusing.
2. Mapleson:
   - Most well-known classification.
   - Five basic systems, A–E, with the addition of a sixth later.[1,2]

3. Miller:
   - South African-trained anaesthetist.
   - Classification based on structure and function.
     - Systems that absorb CO_2.
     - Systems that do not absorb CO_2.[4,5]

Old classification

We can look at the old way of classifying systems to understand the evolution of breathing systems.

- Open system:
  - Systems with no valves, tubing, or reservoir bag.
  - Insufflation.
  - Open drop ether.
  - The patient has access to atmospheric gases.[6]
- Semi-open system:
  - Has a reservoir like a breathing bag and there is no rebreathing.
  - Mapleson circuit.
  - Circle system at high FGF.[6]
- Semi-closed system:
  - Reservoir-like breathing bag that allows for partial rebreathing.
  - Mapleson circuit.
  - Circle system at low FGF.[6]
- Closed system:
  - A system with a reservoir such as a breathing bag allows for complete rebreathing.
  - CO_2 is absorbed.
    - Circle system with pop-off or APL valve closed and very low FGF that equals the oxygen uptake by the patient.[6]

Non-circle systems

Insufflation system

The insufflation system is unpredictable because it is an open system, which means the depth of anaesthesia is difficult to measure. Air entrainment occurs readily, and ventilation cannot be assisted. There is a high risk of fires occurring and gas toxicity within the theatre. Insufflation can be used on a spontaneously breathing patient or controlled ventilation with periods of apnoea.[6]

Examples:

- Oxygen/gases are insufflated over a child's face during induction.
- Gases are insufflated through a catheter or tube placed in the airway.

Open-drop system

Open-drop is an open system where ether or chloroform is dripped onto a mask covered with gauze (Schimmelbusch mask). As the agent vaporises, the mask temperature is lowered. There is a resultant drop in the rate of vaporisation and anaesthetic vapour pressure.[6]

Draw-over system

The draw-over system consists of a nonrebreathing valve, a self-inflating bag, and a vaporisation chamber. Room air acts as a carrier gas and supplemental oxygen is given to increase inspired oxygen (FiO_2) using a tube attached to a T-piece. They can be adjusted for intermittent positive pressure ventilation (IPPV) and continuous positive airway pressure (CPAP), as well as passive scavenging.

The draw-over system has the advantage of being portable, thus it is easily used in locations where compressed gas is not available (developing countries and battlefields).[6]

Unidirectional valve system

This valve system allows for controlled ventilation with a nonrebreathing valve. It is used with respirators or portable manual respirators (Ambu bag). Fresh gas is directed to the patient via a valve and exhaled gas is released into the atmosphere or scavenging system.[6]

Mapleson circuits

These circuits are flow-controlled or CO_2 washout circuits. They rely on FGF for washing out CO_2. The position of the basic components (face mask, fresh gas inflow, spring-loaded pop-off valve, reservoir bag) in the circuit determines the circuit's efficiency. There are six Mapleson circuit types, A–F.[1,6]

Mapleson A

The Mapleson A system is most efficient when used for a spontaneously breathing patient. It conserves exhaled dead space gas and vents exhaled alveolar gas (about FGF 70–80 mL/kg/min). It is not useful in controlled ventilation because it is inefficient (FGF > 2–3 × minute volume [MV]).[1]

As a modification, the coaxial Lack circuit was introduced in 1976. This modification to the Mapleson A circuit has a separate expiratory limb to facilitate gas scavenging and prevent operating room pollution. In this circuit, the respiratory limb runs parallel to the inspiratory limb, or in the coaxial configuration, the expiratory limb runs concentrically inside the inspiratory limb.[1,3]

Mapleson B and C

Mapleson B and C circuits are junctional reservoir systems. Mapleson B is no longer used. Mapleson C is sometimes used for resuscitation or transport along short distances. Both circuits require high gas flow to prevent rebreathing (FGF 20–25 L/min) and create a lot of theatre pollution.[1]

Mapleson D

The Mapleson D system is not efficient for spontaneously breathing patients. If FGF is not high enough, exhaled gas enters the reservoir bag together with fresh gas. It is useful for IPPV (FGF 70 mL/kg/min) as alveolar gas is vented through the expiratory valve and dead space gas is exhaled into the reservoir bag.[1]

Bain's circuit, a coaxial circuit, was created in 1972 and allows easy control of the expiratory valve and scavenging. FGF is delivered at the patient end, allowing the tubing to be longer without increasing dead space, which is useful in providing anaesthesia from a safe distance (e.g. magnetic resonance imaging). It is important to note that disconnection, kinking, and leaks of the inner tubing can lead to the breathing of exhaled gas.[1] Therefore, several checks need to be performed on Bain's circuit:[7]

- Visual inspection: For leaks or disconnection of inner tubing.
- Occlusion test: The Bain circuit is connected to a common gas outlet, flow is applied at 2 L/min, and then the inner tube is occluded with a plunger from a 2 ml syringe. If there is no leak, the bobbin of the flow meter will drop slightly due to increased back-pressure and return to its original position once the occlusion is removed.
- Ghani's test: A modification of the occlusion test, the inner tube is occluded with a 2 ml syringe and on removing the plunger tip a hissing sound should be heard for two to three seconds due to the release of pressure. If this does not occur, there is a hole.
- Pethick's oxygen flush test: The circuit is connected to a common gas outlet, the reservoir bag is filled with oxygen and the circuit is flushed with oxygen using the flush button. If there is no leak the reservoir bag collapses due to the Venturi effect.

Mapleson E

This circuit was developed in 1937. It is a low-resistance breathing system for paediatric anaesthesia (up to 30 kg). FGF of 2–3 × MV is required to prevent rebreathing. To prevent the dilution of gases with room air, the volume in the efferent reservoir limb must be greater than the tidal volume. Intermittent occlusion of the reservoir limb outlet allows for ventilation.[1,3]

Mapleson F

Mapleson F is a modification of Mapleson E (Jackson Rees 1950). It has the addition of an open-ended 500 ml bag to the expiratory limb, allowing for easy manual ventilation and monitoring of respiration by observing the movements of the bag. FGF for spontaneous ventilation is 2–3 × MV.[1]

Humphrey ADE

This circuit allows for changing between the A, D and E modes of the Mapleson circuit. It is suitable for all patient populations. The modification of the system is the addition of a soda lime canister.

Traditional circle systems

These are unidirectional breathing systems. CO_2 is absorbed and these systems allow for partial or total rebreathing of exhaled gases. FGF from the machine passes a one-way valve and is inhaled by the patient. As the patient exhales, the gases from the patient pass another one-way valve, the APL valve, and a reservoir bag, eventually passing the soda lime where CO_2 is absorbed and the gas is mixed with FGF and delivered to the patient again. This is a circle system. They can be semi-open, semi-closed, or closed.[3]

Traditional circle systems have various components:

- FGF tubing from the anaesthesia machine that does not enter the system between the expiratory valve and the patient.
- Inspiratory and expiratory valves for unidirectional flow.
- Inspiratory and expiratory corrugated tubing.
- Y-piece connector.
- Overflow/pop-off valve/APL valve located downstream of the expiratory valve.
- Reservoir bag and ventilator.
- Canister with CO_2 absorbent.[6]

Advantages of circle systems:

- Ability to maintain constant gas concentrations.
- Keeps respiratory moisture and heat within the system.
- Scavenger systems reduce theatre pollution.
- Used for closed-system anaesthesia or semi-closed with low FGF.

Disadvantages of circle systems:

- The circuit is often not checked or not checked properly.
- Lots of connections mean a high risk of disconnection, obstruction, or leaks leading to hypoventilation or barotrauma.
- Malfunction of the unidirectional valve can be deadly:
  - Rebreathing can occur if valves are stuck open.
  - Total blockage of the circuit can occur if the valves are stuck shut.
  - Breath stacking, barotrauma, or volutrauma can occur if the expiratory valve is stuck in the closed position.
- The circle system can fail:
  - A manufacturing defect, debris, patient secretions, particulate obstruction, or blocked filters can cause system failure.
  - This can cause increased airway pressure and haemodynamic instability, bilateral tension pneumothorax.
  - Loss of tidal volume from mechanical dead space.[6]

Soda lime

CO_2 is removed from these breathing systems using soda lime in a canister. Soda lime is a mixture of calcium hydroxide, sodium hydroxide (5%), potassium hydroxide (1%) silicates for binding (< 1%), pH indicator dye, and a 14–19% water content. The

indicator dye contained in soda lime is ethyl violet, which turns from white to purple. Other dyes turn from pink to white.[3]

CO_2 is absorbed after a series of chemical reactions:

- $H_2O + CO_2 \leftrightarrow H_2CO_3 \leftrightarrow H + HCO_3$-
- NaOH (or KOH) + $H_2CO_3 \leftrightarrow NaHCO_3$ (or $KHCO_3$) + H_2O (+ heat) [fast]
- $2NaHCO_3$ (or $KHCO_3$) + $Ca(OH)_2 \leftrightarrow 2NAOH$ (or KOH) + $CaCO_3$ [slow]

Soda lime granules are 4–8 mesh (this means they will fit between a mesh of 4–8 strands per inch^2). If granules are too small dust may be inhaled, and if they are too big the efficiency of CO_2 absorption will be affected.[3]

Problems with soda lime include the production of carbon monoxide, they can absorb volatile agents and release them later leading to slower induction and emergence.[3] Additionally, soda lime produces a substance known as Compound A, a by-product of the absorption of volatiles, which is nephrotoxic in animals.

Conclusion

Anaesthesia breathing systems are complex but important, they keep patients alive. A good understanding of their complex nature and history is important for safe anaesthetic practice.

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References

1. Kaul TK, Mittal G. Mapleson's breathing systems. Indian J Anaesth. 2013;57(5):507-15. https://doi.org/10.4103/0019-5049.120148.
2. Mapleson WW. Anaesthetic breathing systems - semi-closed systems. BJA CEPD Reviews. 2001;1(1):3-7. https://doi.org/10.1093/bjacepd/1.1.3.
3. Tsim P, Howatson A. Breathing systems in anaesthesia. WFSA; 2016. Available from: https://resources.wfsahq.org/atotw/breathing-systems-in-anaesthesia/. Accessed 12 January 2022.
4. Miller DM. Breathing systems for use in anaesthesia: evaluation using a physical lung model and classification. Br J Anaesth. 1988;60(5):555-64. https://doi.org/10.1093/bja/60.5.555.
5. Miller DM. Breathing systems reclassified. Anaesth Intensive Care. 1995;23(3):281-3. https://doi.org/10.1177/0310057X9502300302.
6. Ved S. Circle and noncircle systems. In: Freeman BS, Berger JS, editors. Anesthesiology core review: part one basic exam. New York: McGraw-Hill Education; 2014.
7. Szypula KA, Ip JK, Bogod D, Yentis SM. Detection of inner tube defects in co-axial circle and Bain breathing systems: a comparison of occlusion and Pethick tests. Anaesthesia. 2008;63(10):1092-5. https://doi.org/10.1111/j.1365-2044.2008.05568.x.

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FCA REFRESHER COURSE

Lung function testing and interpretation

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"Remember, when life gets too much… take a spirometric breath." – Farriel Desai

Introduction

Pulmonary function tests (PFTs) are non-invasive tests that indicate how well or poorly an individual's lungs are functioning. PFTs aid the diagnoses of symptomatic disease, screen for early asymptomatic disease, monitor any response to pharmacological therapy, and provide a prognosis for a known disease. PFTs can only provide a physiological diagnosis and not a clinical diagnosis of pulmonary disease. It is important to recognise that a PFT is not a standalone test. A combination of the clinical picture of a patient with other diagnostic tests (arterial blood gases, chest X-rays, etc.) must be made to make a clinical diagnosis of pulmonary disease, particularly if there is a high index of suspicion for disease but PFTs are interpreted as normal.[1]

A major limitation of PFTs is how they are interpreted. Firstly, a knowledge of whether the PFT is acceptable to interpret is important. Secondly, there are many values in the report, therefore it is important to have an organised approach to interpreting these values. Finally, an appreciation that the reference values in PFTs are not absolute cut-off values for confirmed disease is important. A task force appointed in 2022 by the European Respiratory Society (ERS) and the American Thoracic Society (ATS) has updated the 2005 guidelines on PFT interpretation.[2] This refresher will highlight the important updates on reference values, bronchodilator responsiveness interpretation, and the grading of severity of pulmonary disease.

PFTs can comprise six different tests: spirometry, spirometry pre- and post-bronchodilator, flow-volume loop, lung volumes, diffusing capacity for carbon monoxide/transfer factor for carbon monoxide (DLCO/TLCO), and a bronchoprovocation challenge.[1] The number of tests a PFT report may contain will depend on the result of the first basic PFT, namely spirometry.

Reference equations in PFTs (important to understand)

The crux of interpreting PFTs lies in comparing an individual's PFT result to a set of reference values. Reference values are based on reference equations obtained from a population of healthy individuals, which adjust for standing height, biological sex, and age.[2] Ideally, an individual should be compared to their ancestral population of reference equations.

Previously, a major limitation of reference equations was that they were not standardised, adjustment factors were used for black and Asian people and over 100 different reference equations were used for different populations and each PFT. This created uncertainty when interpreting PFTs.[2]

The 2022 ERS/ATS guidelines have now recommended the use of the Global Lung Function Initiative (GLI) reference equations for spirometry, DLCO, and lung volumes. The GLI reference equations consist of five population groups: black, white, North Asian, South Asian, and "other", facilitating a consistent and standardised approach to PFT interpretation across a wider age range than before (3–94 compared to 8–80 years).[2]

Limits of normal

In a healthy population, according to the normal distribution curve, an individual may fall on the fifth percentile of normal, i.e. there is a 5% chance an individual has a low PFT score, which is normal for that individual and not pathological (false positive). This emphasises the uncertainty in interpreting PFTs and allows for a trade-off in incorrectly labelling a low PFT score in a healthy individual as pathological. A fifth percentile equates to a z-score of -1.645, which is considered the lower limit of normal (LLN) in PFTs. The LLN is considered the "cut-off" value in PFT. Conversely, a 95th percentile equates to a z-score of +1.645, which is the upper limit of normal (ULN) for PFTs.[2]

Reference equations for PFTs should be reported as z-scores/LLN and the specific reference equations used should be specified in the PFT reports. For ease of reference in this refresher, LLN and ULN will be used in the discussion below.

PFTs

Spirometry

- Definition: The volume of air (litres) maximally exhaled is measured over different points of time (seconds) after a maximal inhalation to provide peak expiratory flow (PEF),

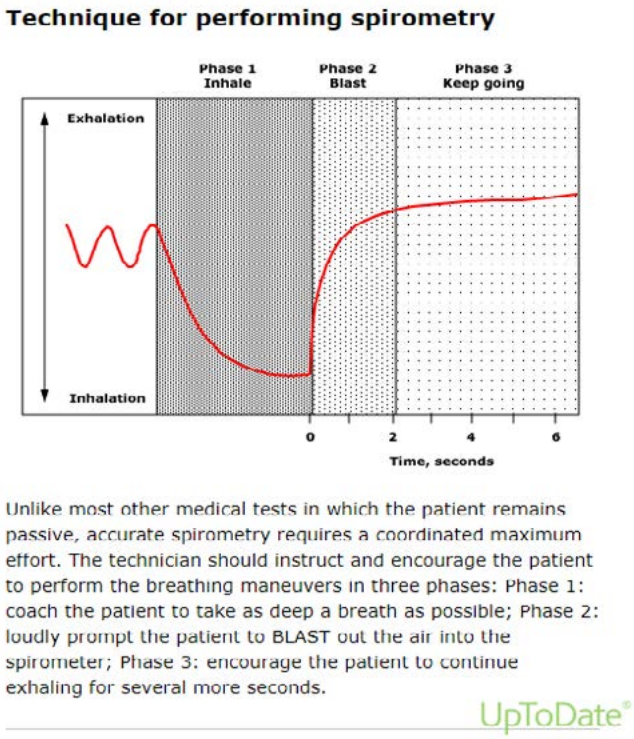

Figure 1: Technique for performing spirometry

forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), the ratio of FEV_1:FVC, and forced mid-expiratory flow ($FEF_{25–75\%}$).

- The technique has three phases (Figure 1):

Phase 1: A nose clip is applied to the nose to prevent an air leak, the patient is coached to inhale as deeply as possible, and a mouthpiece is then placed into the mouth.[3]

Phase 2: The patient exhales forcefully.[3]

Phase 3: The patient continues to exhale forcefully until either a plateau in exhalation or 15 seconds is reached. The spirometry must be acceptable and reproducible.[3]

- Acceptability
  - Good effort with a demonstrable rapid increase in airflow as exhalation begins.
  - The patient must complete the manoeuvre with exhalation lasting at least six seconds to end in a plateau.
- Reproducibility
  - Three efforts are recorded with all three FEV_1 and FVC within 200 ml of each other.
- Interpretation
  - Obstructive lung disease
    - FEV_1:FVC ratio < LLN and PEF < LLN.
    - Note the use of a fixed ratio FEV_1:FVC < 70% to define obstruction and > 80% to define normal is no longer recommended.[2]
    - Spirometry has a "scooped" shape in early obstructive airway disease where the FEV_1:FVC ratio may be normal. $FEF_{25–75\%}$ < LLN.[2]

The current recommendation for the severity of obstruction is to use an FEV_1 z-score if available; the FEV_1 percentage predicted is used, as before, if the FEV_1 z-score is not available (Figure 2).[2]

Spirometry pre- and post-bronchodilator (BDR)

- Indication: To evaluate obstructive lung disease.
- Technique: Chronic pre-existing BDR medication is omitted before spirometry, according to Table I:

Table I: Omission of bronchodilator use prior to PFT

Bronchodilator	Time omitted before PFT
Short-acting β2 agonists (salbutamol)	4–6 hours
Muscarinic antagonists (ipratropium)	12 hours
Long-acting β2 agonists (salmeterol)	24 hours
Ultra-long-acting β2 agonists (indacaterol)	36 hours
Long-acting muscarinic antagonists (glycopyrrolate)	36–48 hours

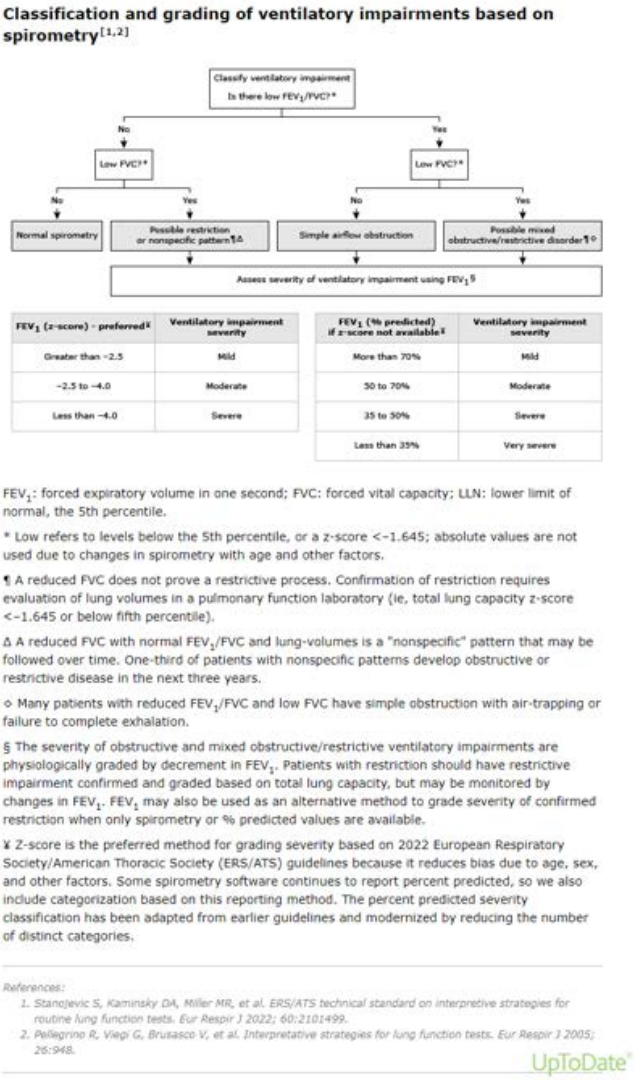

Figure 2: Classification and grading of ventilatory impairments based on spirometry

Albuterol via a spacer/chamber/nebuliser is administered to the patient to assess for reversibility or responsiveness. Spirometry is then repeated after 10–15 minutes.

- Interpretation
  - If a patient has symptoms of asthma but their spirometry is normal, a bronchoprovocation test is done (see bronchoprovocation).[1]
  - Some patients with asthma improve to normal spirometry values post-BDR, these patients have reversible airway disease.
  - Some patients with asthma show an improvement in spirometry values post-BDR, these patients are BDR-responsive.
  - Some patients experience a subjective improvement in symptoms post-BDR; however, their spirometry values do not show an improvement post-BDR. This could be due to an improvement in small airway resistance in response to BDR with no improvement in larger airway resistance post-BDR. These patients should still benefit from a trial of BDR and glucocorticosteroid therapy despite no change in spirometry.
  - Patients with chronic obstructive pulmonary disease (COPD) do not show reversibility in spirometry values post-BDR.
  - Significant response
    - ERS/ATS define a significant post-BDR response as either an FEV_1 or an FVC ≥ 10% of predicted values, respectively. This has changed from greater than 12% and greater than 200 ml. This new ULN is based on worldwide data, excludes age and height as confounders, and is associated with mortality.[2]

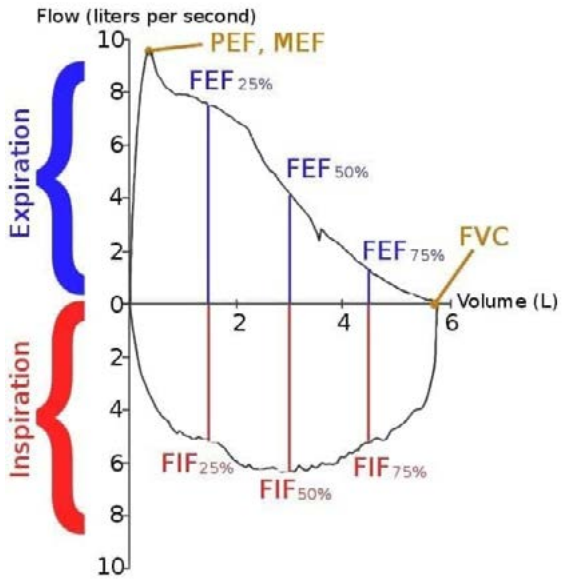

Figure 3: Flow volume loop showing upper exhalation phase (top part of loop) and lower inhalation phase (bottom part of loop). Source: Life in the Fast Lane

    - Equation:

$$\text{BDR response} = \frac{(\text{post-BDR predicted value [L]}) - (\text{pre-BDR predicted value [L]}) \times 100}{\text{Predicted FEV1/FVC value (L)}}$$

*Note that the *actual* BDR predicted value in litres is used, *not* the percentage predicted value for BDR

Flow volume loop

- Definition: The flow of air (litres/second) is measured against lung volumes (litres).
- Technique: The same spirometry technique described above with an additional deep *inhalational* manoeuvre, which must be reproducible, reflecting forced inspiratory vital capacity (FIVC). This is performed at the end of Phase 3 of spirometry, and therefore, a flow volume loop must be specifically requested. Otherwise, a request for spirometry may only provide an exhalation phase (top part of the loop, Figure 3).
- Indication: This PFT assists in determining the cause of stridor/upper airway obstruction/extrathoracic airway obstruction, i.e. pharynx, larynx and trachea above the thoracic inlet.
- Result
  - Variable upper airway obstruction. There is limited airflow during forced inhalation (box-shaped inspiratory pattern on flow-volume loop, Figure 5). During spontaneous ventilation, the negative intraluminal pressure (relative to atmospheric pressure) causes the extrathoracic pathological site to collapse on inhalation (Figure 4A).[1]
  - Variable lower airway obstruction. There is limited airflow during forced exhalation (box-shaped expiratory pattern on flow-volume loop, Figure 5). During spontaneous ventilation, positive intrapleural pressure (relative to intraluminal pressure) causes the intrathoracic pathological site to collapse on exhalation (Figure 4B).[1]
  - Fixed airway obstruction. There is limited airflow during both forced exhalation and inhalation (box-shape inspiratory and expiratory patterns on flow-volume loop).

It is important to note that a pathological tracheal lumen diameter of < 1 cm is required before this pattern is seen on a flow-volume loop, therefore the flow-volume loop has poor sensitivity to diagnose a fixed-upper airway obstruction.[1]

Lung volumes

An understanding of respiratory physiology is needed to relate why changes in certain lung volumes indicate certain lung pathology.[4] Respiratory physiology will not be discussed in this refresher.

- Definitions
  - Volumes (Figure 6)
    - Tidal volume (TV): Normal breathing (± 500 ml).
    - Inspiratory reserve volume (IRV): Extra air which can be inhaled beyond a TV breath (± 3 000 ml).

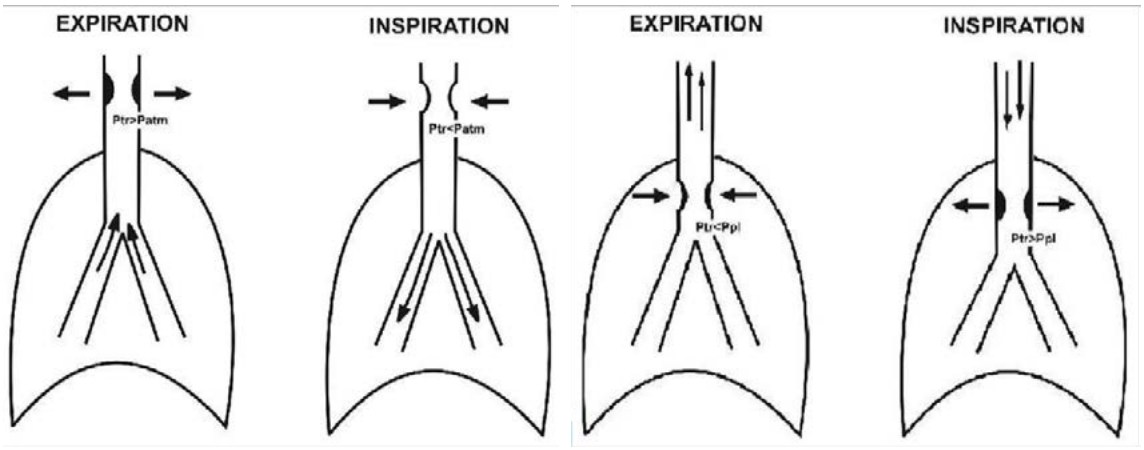

Figure 4.A (left): Variable upper airway obstruction, **Figure 4.B** (right): Variable lower airway obstruction. Source: Researchgate

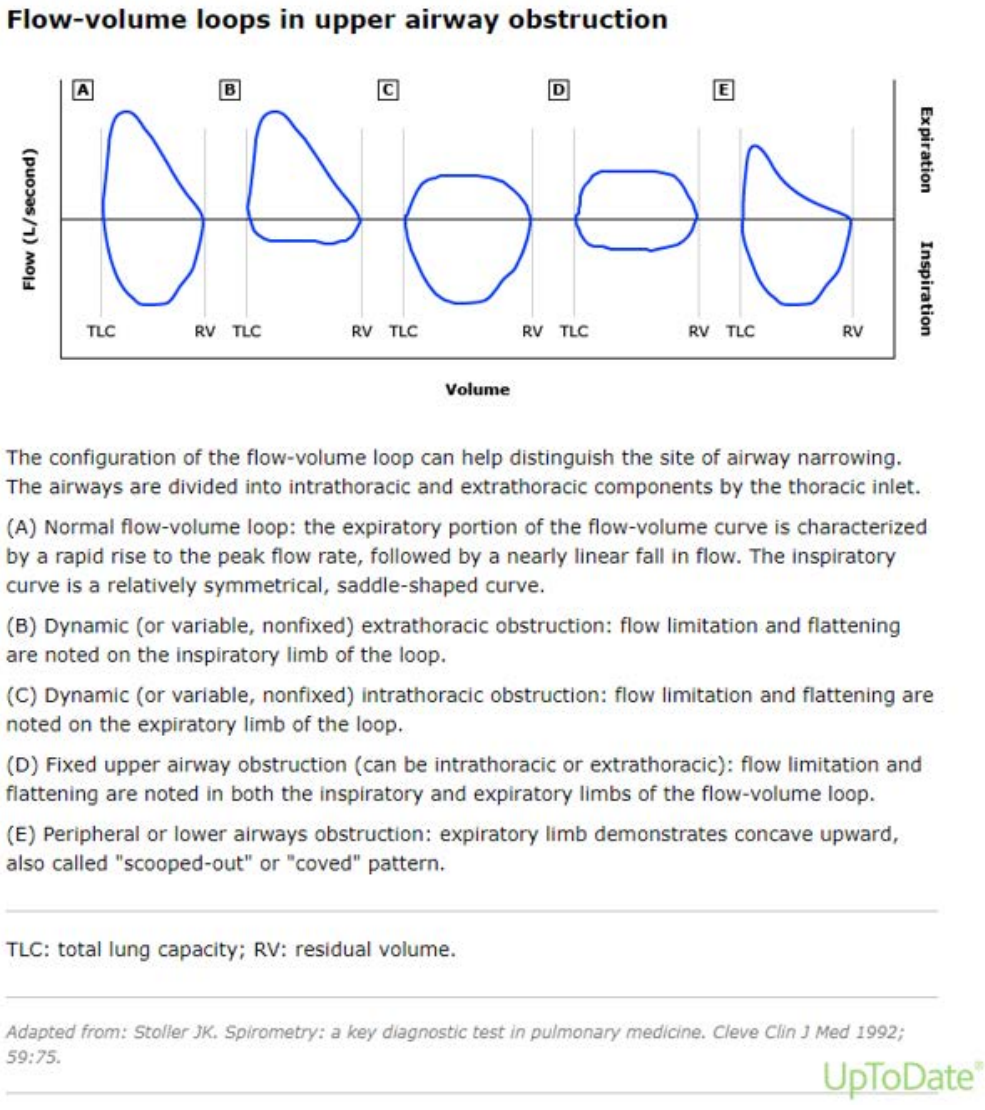

Figure 5: Flow-volume loops in upper airway obstruction

- Expiratory reserve volume (ERV): Extra air which can be forcefully exhaled beyond a TV breath (± 1 100 ml).
- Residual volume (RV): Volume of air remaining in the lung after a maximal exhalation (± 1 200 ml).

◦ Capacities (sum of volumes, Figure 6)

- Inspiratory capacity (IC): TV + IRV.
- Expiratory capacity (EC): TV + ERV.
- Functional residual capacity (FRC): ERV + RV.
- Vital capacity: IRV + TV + ERV (total amount of exchangeable air).
- Total lung capacity (TLC): IRV + TV + ERV + RV (total amount of air in the lung after a maximal inhalation effort).

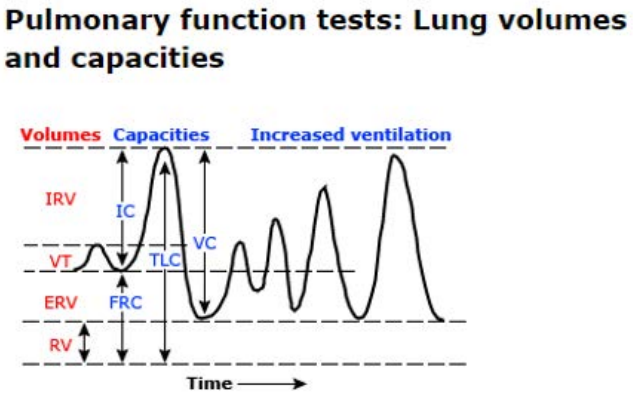

Figure 6: PFTs: lung volumes and capacities. Source Life in the Fast Lane

- Indication: When there is a decreased FVC on spirometry, this PFT is done to determine if a low FVC is due to a restrictive lung disease, severe obstruction, neuromuscular disease or poor effort from the patient. It also differentiates between chronic bronchitis and emphysema as the cause of airway obstruction.[1]
- Technique: There are four ways to measure lung volumes, namely body plethysmography (the gold standard and may overestimate lung volumes), helium dilution, nitrogen washout (may underestimate lung volumes), and chest imaging. These techniques are topics to be studied under physics and will not be discussed in detail here.
- Interpretation
  - Restrictive lung disease: TLC < LLN.
  - Mixed disease (obstructive and restrictive pattern): FEV_1:FVC ratio < LLN plus TLC < LLN.
  - Air trapping (clinically precedes hyperinflation): RV > ULN with a normal TLC or RV:TLC ratio is increased.
  - Hyperinflation: FRC and/or TLC > ULN.
  - Non-specific pattern: FVC is low but FEV1:FVC ratio and TLC are both normal.

Diffusing capacity for carbon monoxide quantitation (DLCO) or transfer factor for carbon monoxide (TLCO)

- Indication
  - Evaluate whether obstructive lung disease (FEV_1:FVC < LLN) is due to emphysema or chronic bronchitis.
  - Evaluate if restrictive lung disease (TLC < LLN) is due to intrinsic lung disease or extrinsic lung disease.
  - Evaluate if there is pulmonary vascular disease.
- Technique
  - A single breath test where the patient exhales deeply to RV and a device connected to a test gas (0.3% carbon monoxide [CO], tracer gas, oxygen, and nitrogen) is placed in the patient's mouth. The patient then inhales to TLC in four seconds, holds their breath for 10 seconds and then exhales to RV rapidly. An alveolar gas sample is taken, dead space is washed out, and CO uptake is calculated.
  - Adjustments are made for anaemia (low haemoglobin reduces the carrying capacity for CO in blood, resulting in poor CO uptake) and smoking (carboxyhaemoglobin reduces the carrying capacity of haemoglobin for CO).
- Interpretation (Figure 7)
  - Emphysema: DLCO < LLN.
  - Chronic bronchitis: DLCO is normal.
  - Intrinsic lung disease: DLCO < LLN.
  - Extrinsic lung disease: DLCO is normal.
  - Pulmonary vascular disease: Normal spirometry plus DLCO < LLN.

Bronchoprovocation challenge

(This topic will not be discussed in detail in this refresher.)

- Indications
  - Reversible airway disease is suspected but normal spirometry is obtained.
  - Variable airflow limitation is present (only after certain triggers are encountered).
  - Airway hyperresponsiveness due to inflammation or specific external triggers.

Interpretation of diffusing capacity of the lungs for carbon monoxide (DLCO)

Increased DLCO
Altitude
Asthma
Polycythemia
Severe obesity
Pulmonary hemorrhage
Left-to-right intracardiac shunting
Mild left heart failure - increased pulmonary capillary blood volume
Exercise just prior to the test - increased cardiac output
Mueller maneuver
Supine position
Low DLCO with normal spirometry and normal lung volume
Anemia - mild decrease
Pulmonary vascular disease - mild to severe decrease
Early interstitial lung disease - mild to moderate decrease
Valsalva maneuver
Low DLCO with obstruction with or without concomitant restriction
Bronchiolitis
Combined pulmonary fibrosis and emphysema (CPFE)
Cystic fibrosis
Emphysema
Interstitial lung disease in patient with COPD
Lymphangioleiomyomatosis
Sarcoid
Low DLCO with restriction
Interstitial lung disease
Pneumonitis
Other
Carboxyhemoglobin - reduces DLCO
Supplemental oxygen - reduces DLCO
Bronchodilator - increases DLCO

UpToDate

Figure 7: Interpretation of diffusing capacity of the lungs for carbon monoxide (DLCO)

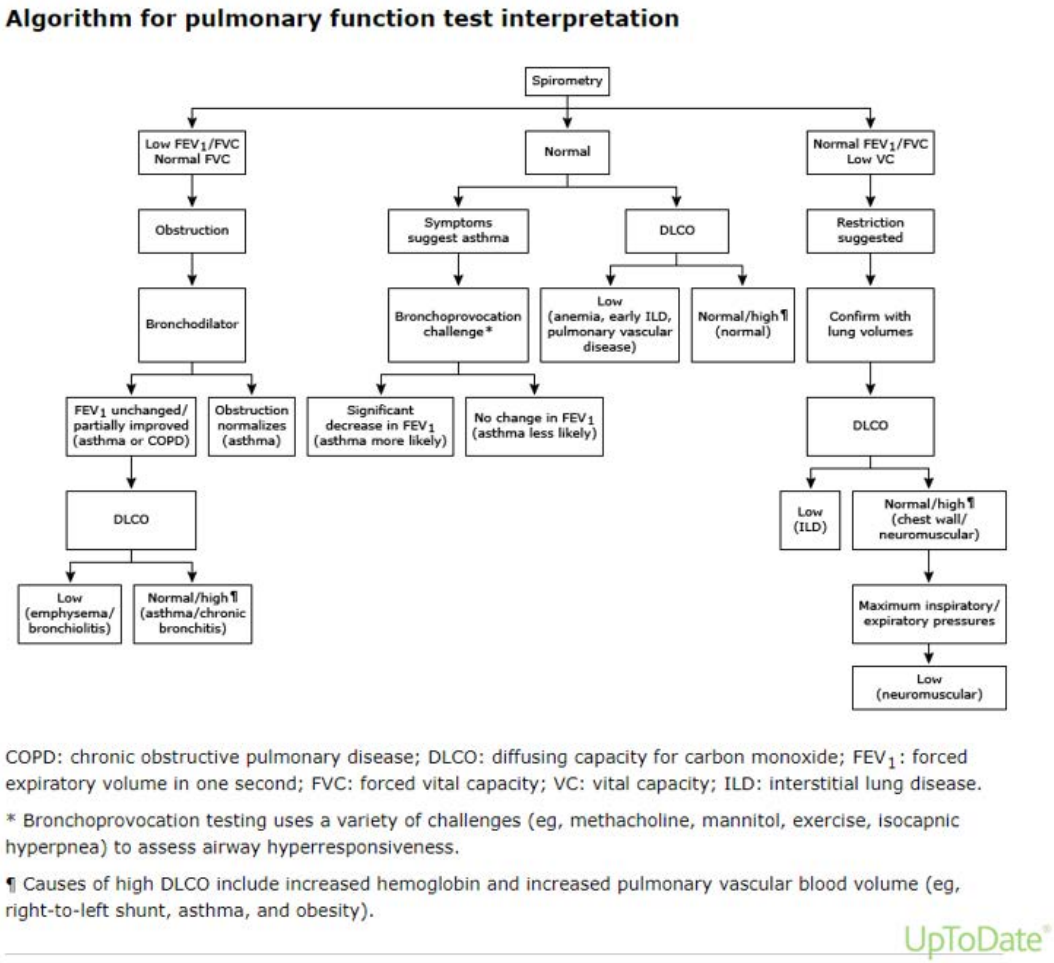

Figure 8: Algorithm for PFT interpretation

- Methacholine, mannitol, and exercise are used to stress the airways.

Practise (remember to have a system, Figures 8 & 9)

1. What is the clinical scenario of the patient? Look at the demographics (this is important).
2. Start with analysing the flow-volume loop and the volume-time curve.
3. Identify any obvious patterns; is the loop acceptable and reproducible?
4. Are the reference equations mentioned in the report?
5. Look at the values of FEV_1 and FVC compared to LLN and work out BDR response if BDR is used.
6. Work out FEV_1:FVC ratio.
7. Are lung volumes available? Assess the TLC for restrictive lung disease.
8. Is there a DLCO available?

COVID-19

PFTs are aerosol-generating procedures. With the recent COVID-19 pandemic, it is recommended to only perform PFTs if they are vital to aiding diagnostic and management decisions (e.g. pneumonectomy).[1] There are several strategies to limit the spread of aerosols.

- Patient
  - Select appropriate patients for PFTs.
  - Patients should not be queued for prolonged periods.
  - A delay of 20 minutes to three hours between patients to allow for the elimination of aerosols.
- Staff
  - Hand washing and use of personal protective equipment (N95 mask, apron, face shield, and gloves).
- Equipment
  - Single-use mouthpieces and disposable filters.
  - Negative pressure rooms with frequent air changes.

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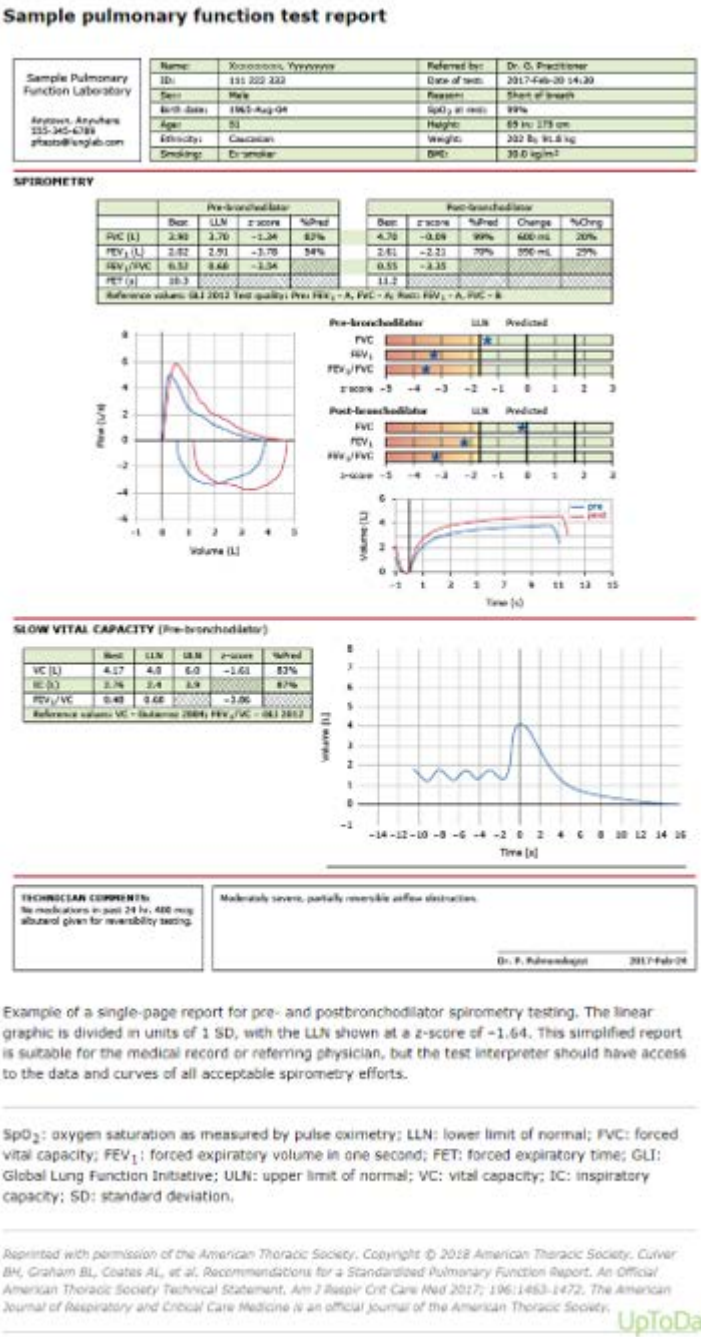
References

1. Kaminsky DA. Office spirometry. UpToDate; 2023. Available from: https://www.uptodate.com/contents/office-spirometry?search=pulmonary%20function%20testing&topicRef=6969&source=see_link. Accessed 29 August 2023.
2. Kaminsky DA. Overview of pulmonary function testing in adults. UpToDate; 2022. Available from: https://www.uptodate.com/contents/overview-of-pulmonary-function-testing-in-adults?search=pulmonary%20funstion%20tests&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 28 August 2023.
3. Stanojevic S, Kaminsky DA, Miller MR, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J. 2022;60(1):2101499. https://doi.org/10.1183/13993003.01499-2021.
4. Guyton AC, Hall JE. Human physiology and mechanisms of disease. 6th ed. Pennsylvania: Philadelphia; 1997. p. 314-5.



Example of a single-page report for pre- and postbronchodilator spirometry testing. The linear graphic is divided in units of 1 SD, with the LLN shown at a z-score of −1.64. This simplified report is suitable for the medical record or referring physician, but the test interpreter should have access to the data and curves of all acceptable spirometry efforts.

SpO_2: oxygen saturation as measured by pulse oximetry; LLN: lower limit of normal; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; FET: forced expiratory time; GLI: Global Lung Function Initiative; ULN: upper limit of normal; VC: vital capacity; IC: inspiratory capacity; SD: standard deviation.

Figure 9: Sample PFT report

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FCA REFRESHER COURSE

Local anaesthetics

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Keywords: local anaesthetics, inhibit, transmission, nerve impulse

Introduction

Local anaesthetics (LAs) are drugs that reversibly inhibit the transmission of a nerve impulse where they are applied and they can be used as a sole anaesthetic or as analgesia, either intraoperatively or postoperatively.[1] The routes of administration include but are not limited to, topical, subcutaneous, peripheral nerve blocks, and neuraxial.[2]

To accurately and confidently use any LA, one must understand the pharmacology of these drugs as a group and as individuals, as well as the importance of anatomy and physiology.[1] Individual drugs are not discussed in this refresher.

Structure and classification of a LA

The structure of a LA is made up of three parts, a lipid-soluble aromatic group, which is hydrophobic, a hydrophilic amine group, and an intermediary link between the two groups (Figure 1).[2] This intermediary link determines what class the LA drug belongs to; the two types described are esters and amides.[1] Table I describes the characteristics of both groups in comparison to each other.[1]

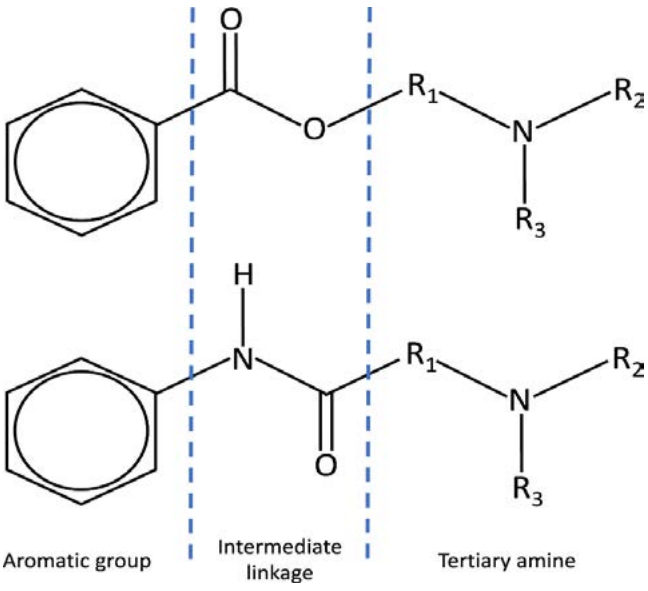

Figure 1: Structure of ester and amide LAs; each contains an aromatic group, an intermediate linkage (ester/amide), and a tertiary amine[2]

Table I: Comparisons of differences between ester and amide LAs[1]

Esters	Amides
Unstable in solution	Stable in solution
Shorter storage period	Longer storage period
Metabolised by plasma cholinesterase	Hepatic metabolism via microsomal hepatic systems
Rapid metabolism	Slow metabolism
More allergic reactions were seen due to the production of PABA	Rare allergic reactions
E.g. cocaine, procaine, benzocaine, tetracaine	E.g. lidocaine, bupivacaine, ropivacaine, prilocaine

The aromatic group is crucial for the anaesthetic activity because it is involved in the attachment of the drug to the sodium-channel site.[3]

Mechanism of action

The main theory described is the blockage of voltage-gated sodium-channels (VGSC) intracellularly by the LA. Other theories, which are beyond the scope of this update, propose ion-channel involvement (potassium and calcium) and receptor involvement (transient receptor potential vanilloid subtype 1 channel).[3] These theories are believed to be the reason for the other actions of LAs, such as their anti-inflammatory action and analgesic action along with their side effects.[4]

Neural transmission

The nerve fibre has a resting membrane potential between -50 mV and -90 mV, which is maintained by the sodium-potassium (Na/K) ATPase pump found as an integrated membrane in the lipid bilayer of the cell. This sodium-channel has a gate mechanism that can be found in three states, resting (meaning the channel is closed), activated (the channel is open), and inactivated (the channel is closed).[3]

Stimulation of the nerve causes an increase in permeability to sodium and changes the configuration of the sodium-channel from closed to open, this causes the nerve to be depolarised and the membrane potential increases to +20 mV due to an influx of sodium into the cell. The sodium inflow ceases when the electrochemical and concentration gradients of sodium are equal, at this point the sodium-channel is inactive and the

potassium efflux starts, which repolarises the nerve to its resting state.[3,5] The Na/K pump will then restore the concentration gradients and the resting membrane potential.[5]

Effect of LAs

LA drugs are weak bases, therefore a large proportion is in an ionised state. Only the un-ionised form of the LA can cross through the lipid membrane and enter the cell. The LA then dissociates again in the cell and reaches a new equilibrium of ionised and un-ionised forms according to the intracellular pH and the pKa of the LA (pKa will be discussed later).[2] The ionised form inside the cell then binds to the open VGSC. This binding increases with the frequency of nerve depolarisation so high-activity nerves are easily blocked in a phenomenon called use-dependant block.[2]

Physicochemical properties of LAs

The physiochemical properties of the drug, as determined by the aromatic structure and the length of the hydrocarbon chain, affect the function of the LA.[1] Any changes to the basic structure of these drugs, whether by lengthening the intermediate group or changing the number of carbon atoms, will entail a change in the drug's activity regarding things such as the onset of action, duration of action, potency, etc.[3] Table II summarises the physiochemical properties of LAs.

The anatomy of the nerve also contributes to the physiochemical properties of a LA; the more easily blocked the nerve, the faster the onset of action:[3]

- Nerves that fire more frequently or are used often tend to be more amenable to sodium blockage, therefore they are more easily blocked.
- Nerve fibres with a small diameter are blocked more easily.
- Myelinated fibres are more easily blocked compared to unmyelinated ones.

Pharmacokinetics

Absorption

The regional blood flow determines how much of the LA will be taken up into the systematic circulation.[3] The more vascular the area into which the LA is injected, the more rapid the uptake. The order from the highest absorption from a single dose is intrapleural > intercostal > lumbar epidural > brachial plexus > subcutaneous.[2] The vasoactivity of a LA may sometimes prevent this; it has been shown that at low doses LAs are vasodilatory, thus increasing their absorption.[2] Other factors to consider are the site of injection, the rate of injection, drug tissue binding, and the dose of the drug given as repeated dosing or a high single dose contributes to toxicity.[3,8]

Distribution

Distribution is influenced by protein binding.[1] Ester LAs are more protein-bound than the amide LAs, therefore they have a longer duration of action.[2] Distribution is also influenced by organ perfusion and the drug/blood partition coefficient, which is influenced by protein binding and lipid solubility.[3]

Metabolism

Esters are metabolised by plasma cholinesterase whilst amides undergo hepatic metabolism via the microsomal hepatic.[1] The administration of other drugs that use the same hepatic system along with a decrease in hepatic blood flow may affect the metabolism of a LA.[8]

Excretion

Ester metabolites are renally excreted and amides excrete very little renally unchanged.[1,2]

Adjuvants

Substances may be added to a LA to:

- preserve the molecules;
- prevent microbial growth;
- prevent systematic absorption;
- prolong or enhance the LA's action; and
- enhance the speed of the LA.[4]

The commonly used adjuvants are adrenaline, dexamethasone, clonidine, opioids, dexmedetomidine, ketamine, and midazolam.[2]

Table II: Physiochemical properties of LAs

Property	Definition	Effect
pKa	The pH where the ionised and un-ionised form of the LA is in equal concentration; also known as the dissociation constant.[3]	The closer the pKa is to serum pH, the greater the concentration of the drug intracellularly binding to the sodium-channels, resulting in a faster onset of action.[3]
Lipid solubility	The ratio of concentrations when LAs are dissolved in a mixture of lipid and aqueous solvents.[2]	The greater the lipid solubility of the drug, the better it can penetrate the cell membrane and have an effect, making it more potent.[1]
Protein binding	This defines the degree of attachment of drugs to the proteins in blood plasma.[6]	The more highly protein-bound, the lower the bioavailability of the LA, and the longer the duration of effect.[2]
Isomerism	Stereoisomers are molecules with identical atomic composition and chemical properties but different spatial arrangements of atoms.[7]	The R-enantiomer seems to be more potent and more toxic compared to the L-enantiomer.[3]

Complications

LA complications include neurotoxicity, muscle damage where they infiltrate, anaphylactic reactions, and local anaesthetic systematic toxicity (LAST). LAST may be due to either an accidental intravascular injection or secondary to a high plasma LA concentration. For this reason, it is important to know the toxic doses of LAs. Table III mentions the maximum doses of some LAs.[3]

Table III: Maximum doses of LAs[3]

Drug	Toxic dose without adrenaline	Toxic dose with adrenaline
Lignocaine	IV: 1–1.5 mg/kg	IM: 7 mg/kg
	S/C or IM: 3–5 mg/kg	
	Topical: 5 mg/kg	
	IVRA: Use 0.5% Upper limb: 0.5 ml/kg Lower limb: 1 ml/kg	Not applicable
Bupivacaine	2 mg/kg (maximum 150 mg)	No benefit
L-bupivacaine	2 mg/kg (maximum 150 mg)	No benefit
Ropivacaine	2 mg/kg (maximum 150 mg)	No benefit

LAST can present with symptoms that either predominantly affect the central nervous system (CNS) or cerebrovascular system (CVS).[3] CNS symptoms arise from the selective inhibition of excitatory CNS pathways.[9] This may manifest as vertigo, tinnitus, circumoral paresthesias, confusion, tremors, myoclonus jerks, convulsions, loss of consciousness, and coma.[9]

CVS toxicity may be from direct or indirect mechanisms. The direct mechanisms are from negative inotropy driven by decreased calcium release from the sarcoplasmic reticulum, disturbances of sodium-calcium pumps, alteration of mitochondrial energy transduction, and delays in impulse conduction through the cardiac conduction tissue. The indirect mechanisms arise centrally from the blockage of outflow impulses of the nucleus tractus solitarius, inhibition of baroreflex sensitivity, and inhibition of the cardiac centre in the midbrain. These will initially manifest as hypertension, tachycardia, decreased cardiac output, hypotension, severe hypotension, sinus bradycardia, ventricular dysrhythmias, and ultimately cardiac arrest.[3]

Treatment of LAST

Intravenous lipid emulsion therapy can either be intralipid or linoleic. Intralipid is a 20% lipid solution that works as a lipid sink, which draws the drug out and binds it, thereby decreasing the amount of LA available to bind receptors. Furthermore, it has a high lipid concentration and acts as a source of energy via long-chain fatty acids; the dose is 1 ml/kg intravenous STAT, and the STAT dose can be repeated twice, followed by an infusion of 0.25 ml/kg/min. Other treatments such as amiodarone, glucose, insulin and potassium infusions, bretylium tosylate, and potassium-channel openers have also been used.[3]

Reversal for LAs

Phentolamine mesylate is a non-selective alpha antagonist and has been used to reverse LA post-dental surgery. It functions by causing vasodilatation, which increases blood flow and increases clearance time.[2]

Resistance to LAs

There are a few reasons why the block performed may fail resulting in inadequate analgesia. These include factors such as:

- wrong expectations or fears by the patient;
- incorrect mode of application;
- errors in dosage;
- product preparation; and
- tissue inflammation.[10]

There are some conditions where true LA resistance may occur:[10]

- Gene mutations associated with the VGSC are suspected to cause LA resistance with possible alteration of nociception and perception of temperature.
- Scorpion stings. The poison is believed to induce antibodies that interact with the LA binding site of the VGSC.
- Ehlers-Danlos syndrome of the hypermobility type, causing altered LA spread.
- Regular opioid use. This is due to multiple mechanisms including changes in the shape, function, and concentration of opioid receptors. The interaction and cross-tolerance between LA and opioid consumers needed higher doses of lidocaine to experience sufficient analgesia during surgical wound treatment.
- Natural red hair. The hypothesis is that there is an increase in central nociception and that the melanocortin 1 receptor gene mutation upregulates central melanocortin, which in turn increases baseline pain.

Other uses of LAs

LAs may also be used to treat acute and chronic pain, inflammation, cancer, and postoperative ileus.[4] However, the evidence for some of these uses is still conflicting.[2]

Conclusion

Given the variety of situations in which one can use LA drugs, it is imperative to have a full understanding of their pharmacology to use them safely and effectively.

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References

1. Edgecombe H, Hocking G. Local anaesthetic pharmacology [Internet]. WFSA; 2005. Available from: http://resources.wfsahq.org/atotw/local-anaesthetic-pharmacology/. Accessed 20 August 2023.
2. Taylor A, McLeod G. Basic pharmacology of local anaesthetics. BJA Educ. 2020;20(2):34-41. https://doi.org/10.1016/j.bjae.2019.10.002.
3. Dippenaar JM. Local anaesthetics. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 1st ed. Centurion: Medpharm; 2012.

4. Heavner JE. Pharmacology of local anaesthetics. In: Longnecker DE, Brown DL, Newman MF, Zapol WM, editors. Anesthesiology. 2nd ed. McGraw Hill; 2012.
5. Wildsmith JAW. Local anaesthetics. In: Aitkenhead AR, Smith G, editors. Textbook of anaesthesia. 2nd ed. London: Churchill Livingstone. p. 257-67.
6. Barton P, Austin RP, Fessey RE. In vitro models for protein binding and tissue storage. Comprehensive Med Chem II. 2007;5:321-40. https://doi.org/10.1016/B0-08-045044-X/00129-2.
7. Whiteside JB, Wildsmith JAW. Developments in local anaesthetics drugs. Br J Anaesth. 2001:87(1):25-37. https://doi.org/10.1093/bja/87.1.27.
8. Drasner K. Local anaesthetics [Internet]. Basicmedical Key; 2016. Available from: http://basicmedicalkey.com/local-anesthetics/. Accessed 21 August 2023.
9. Butterworth J. Clinical pharmacology of local anaesthetics [Internet]. NYSORA. Available from: http://www.nysora.com/topics/pharmacology/clinical-pharmacology-local-anesthetics/. Accessed 20 August 2023.
10. Marti F, Linder G, Ravioli S. Resistance to local anaesthetics: a literature review. Br J Anaesth. 2022;129(2):E43-5. https://doi.org/10.1016/j.bja.2022.05.006.

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FCA REFRESHER COURSE

A tale of two kidneys

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Keywords: renal tubular feedback mechanism, renal system functions

Introduction

Little has changed in our basic physiological understanding of the kidneys in the last 70 years. Indeed, the renal system functions to maintain acid-base homeostasis, eliminate detoxified substances, and regulate the plasma ion concentration and volume in response to endogenous or exogenous stimuli.[1–3] The by-product of these processes is the production of urine, the composition of which changes according to the physiological needs of the individual. Additionally, the kidneys also produce hormones such as renin, erythropoietin, and the active form of vitamin D.[4]

This article serves as a summary of some important concepts that occur relating to renal function: tubuloglomerular feedback, ion exchange in the nephron, and the countercurrent multiplier and exchange systems.

Relevant anatomy (Figure 1)

There are normally two functioning kidneys in the human body located within the confines of the retroperitoneum. Each kidney is made up of about a million specialised, functional units called the nephron. There are two broad groups of nephrons, aptly named for their location either in the cortex or close to the medulla of the kidney. Each nephron has different tubular sections starting with the Bowman's capsule, which houses a tuft of capillaries known as the glomerulus, with its own afferent and efferent arterioles. Together, the Bowman's capsule and glomerulus are referred to as the renal corpuscle. The Bowman's capsule then connects to the proximal convoluted tubule, followed by descending then ascending thick and thin loops of Henle. Finally, the distal convoluted tubule connects the loop of Henle to the collecting duct, which coalesces with other collecting ducts to form the renal pelvis. The renal pelvises drain into the ureter allowing the plasma ultrafiltrate to be escorted to the bladder for safekeeping until excretion. Collecting ducts or tubules have two segments, again named for their location within the kidney – cortical and medullary collecting ducts.[1,2,4]

The juxtaglomerular apparatus (JGA) is a special intersection in the nephron of the kidney where the distal convoluted tubule takes a turn to lie next to the Bowman's capsule. This area of the

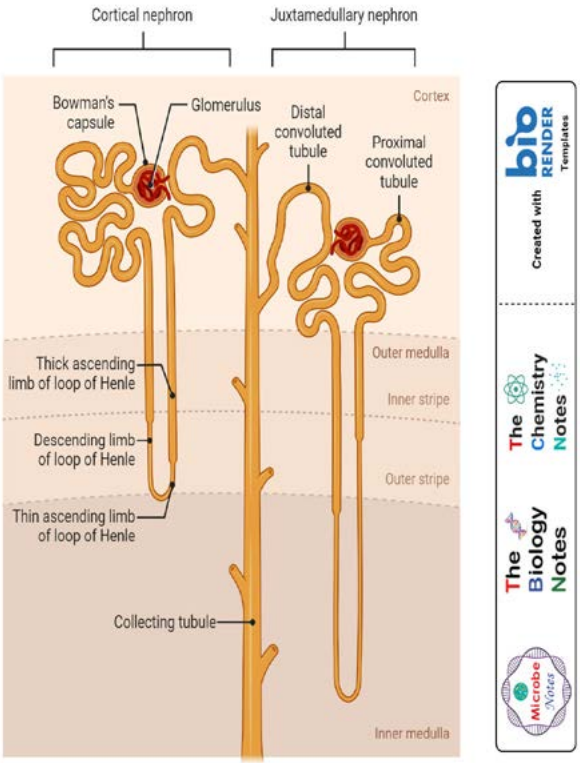

Figure 1: Anatomy of the nephron[5]

distal convoluted tubule contains specialised tubular cells called the macula densa, which are sensitive to changes in sodium and chloride concentrations in the tubular fluid. The apparatus not only houses the macula densa but also contains special smooth muscle arteriolar cells called granular cells, which contain secretory granules.[1,2,4]

Autoregulation

The kidneys do not function independently. There are complex communication channels that regulate the glomerular filtration rate (GFR), ultimately altering renal tubular secretion and reabsorption to maintain homeostasis, somewhat akin to traffic lights at a busy intersection. The GFR refers to the rate at which blood is filtered by the glomerulus in the renal corpuscle. There are two broad mechanisms responsible for maintaining a steady

GFR, the myogenic mechanism and the tubuloglomerular feedback mechanism.[1]

Myogenic mechanism

Smooth muscle cells in the walls of the afferent arterioles of the glomerulus respond to changes in blood pressure. If the blood pressure increases, the arterioles constrict to prevent excessive filtration and with a reduction in blood pressure the arterioles will dilate to maintain an adequate GFR.[1] Specialised cells located between the glomerular capillaries, called mesangial cells, aid in this mechanism by contracting or relaxing in response to signals from the macula densa. Contraction reduces the surface area available for filtration, while relaxation increases it, influencing the GFR.[1]

Tubuloglomerular feedback mechanism

If the GFR rises due to increased blood pressure, there will be a correlating increase in tubular fluid flowing past the macula densa (because more fluid is filtered). As the amount of tubular fluid increases, the amount of sodium filtered also increases. This is sensed by the macula densa and results in the release of adenosine triphosphate (ATP) and adenosine, which act on the afferent arteriole of the glomerulus and cause it to constrict. This afferent arteriolar constriction serves to normalise the GFR once more. If there is a decline in the GFR, the opposite will occur. In a power play, the macula densa also secrete nitric oxide that can stop the action of ATP and adenosine, which would otherwise cause the afferent arteriole of the glomerulus to constrict.[1,4]

Hormonal influences on the GFR

Renin-angiotensin-aldosterone system (RAAS)

This multisystemic feedback mechanism helps regulate the body's fluid balance and blood pressure. Specialised cells in the JGA release renin in response to a decrease in blood pressure or sodium levels. Renin initiates a cascade of events ultimately leading to the cleavage of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II by a converting enzyme and this hormone causes the "angios" to "tense". This intense vasoconstriction is paired with the release of aldosterone from the adrenal glands, which then acts on the distal convoluted tubule and collecting ducts to increase sodium (and thus also water) reabsorption. The result is an elevation of blood pressure due to an increase in circulating blood volume and an increase in systemic vascular resistance via vasoconstriction.[1,4]

Antidiuretic hormone (ADH)

Also known as vasopressin, ADH acts in the collecting ducts to prevent diuresis. It is released from the posterior pituitary gland in response to changes in blood osmolality. In response to ADH release, aquaporins emerge in the cells of the collecting ducts rendering them more permeable to water reabsorption (thus reducing water excretion). The result is water reabsorption and the excretion of concentrated urine.[1,4]

Atrial natriuretic peptide

This hormone is secreted by the atria in the heart in response to high blood pressure. When released, the hormone promotes sodium and water excretion by inhibiting the release of aldosterone. Without aldosterone present, sodium (and water) reabsorption in the distal tubules is reduced.[1,4]

The various renal tubular feedback mechanisms are tightly interconnected and coordinated to ensure overall homeostasis. Changes in blood pressure and fluid balance can alter hormone secretion, directly affecting renal arteriolar tone and thus the GFR. Simultaneously, electrolyte reabsorption or secretion is enhanced to maintain the plasma-ion concentration following the body's needs. Other influences on the GFR, such as calcium homeostasis, sympathetic control, and the role of the baroreceptor reflex, as well as the influence the filtration coefficient can have on the GFR, are not discussed in this summary. Let us now delve deeper into the streets of each segment of the nephron.

Ion exchange mechanisms

Akin to the busy streets of a city, each segment of the nephron is like an intersection with different capabilities in terms of which ions are reabsorbed or secreted into tubular fluid. Additionally, different transport mechanisms facilitate the transport of ions across the cells of different segments of the nephron. Water reabsorption in the nephron generally follows sodium reabsorption, but certain segments of the nephron are impermeable to water unless facilitated by hormonal feedback. We can consider these gated communities where an entrance fee is required.

Transport mechanisms

There are several transport mechanisms used in the nephron to transport ions across cell membranes, either into tubular fluid or back across into the intravascular space (see Figure 2).

Passive diffusion

Ions follow a concentration gradient and move from high to low concentrations.[6] This is similar to the flow of traffic from the central business district (CBD) of a city to the quieter suburbs.

Active transport

Ions move against their concentration gradient and require help in the form of ATP to achieve this. Of importance is the sodium-potassium adenosine triphosphatase pump (Na/K ATPase), which actively transports sodium out of cells and potassium into cells against their concentration gradients.[2] This can be considered analogous to having to go back to work in the CBD and realising there will be no parking, so you hop in a metered taxi.

Secondary active transport (co-transport)

This is the movement of two ions, one down its concentration gradient and one against. The ion moving along its concentration gradient releases the energy required to move the other ion

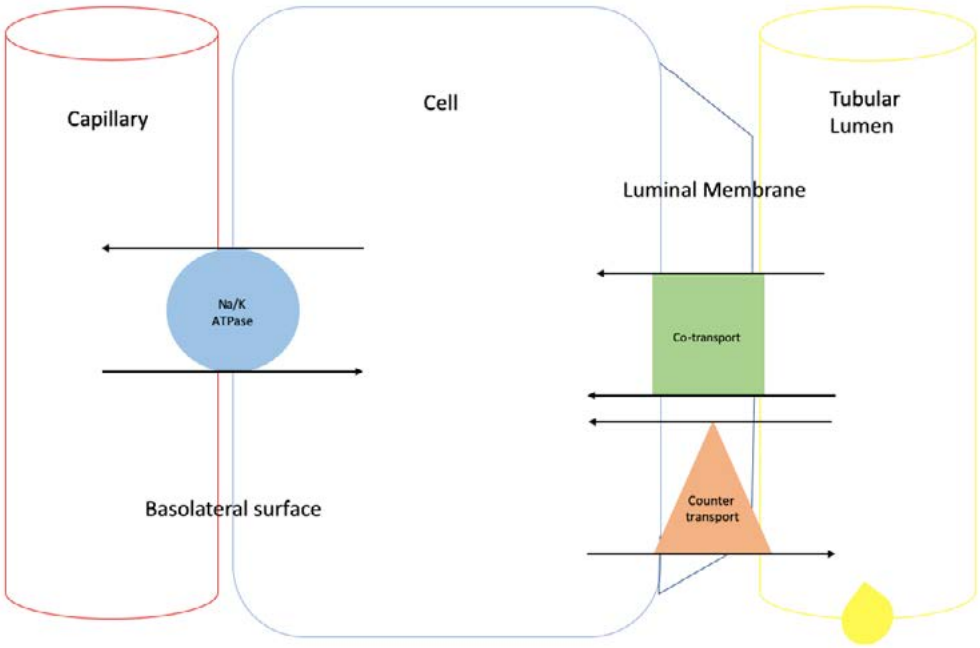

Figure 2: Transport mechanisms common in the nephron

against its concentration gradient.[2] Similar to passengers in a bus, some are going home to quiet suburbs while others are headed in busier directions.

Counter-transport

This transport mechanism moves two ions in opposite directions across a cell membrane.[2] Think of pedestrians crossing the street in opposite directions.

Facilitated diffusion

Ions move across a membrane with the help of carrier proteins. These proteins assist in the transport of specific ions or molecules across a membrane, usually down their concentration gradient.[2] Parents of children will understand that these little ones are best transported from busy areas to quieter areas in a pram.

Paracellular transport

This refers to the movement of ions between cells through the tight junctions that connect cells. This pathway allows for the passive movement of ions based on concentration gradients. This mechanism is particularly important for the movement of water and small ions.[6] Think of the minibus taxi that sneaks past you standing still at a red traffic light.

Ion exchange in the nephron: sodium handling (Figure 3)

Proximal convoluted tubule

Of the sodium load presented to the proximal convoluted tubule, 65–70% is reabsorbed.[4] Sodium gains entrance into the tubular cell across the luminal membrane via two mechanisms. The first is co-transport with nutrients and the second is counter-transport with hydrogen ions, or ammonium. Both of these transport

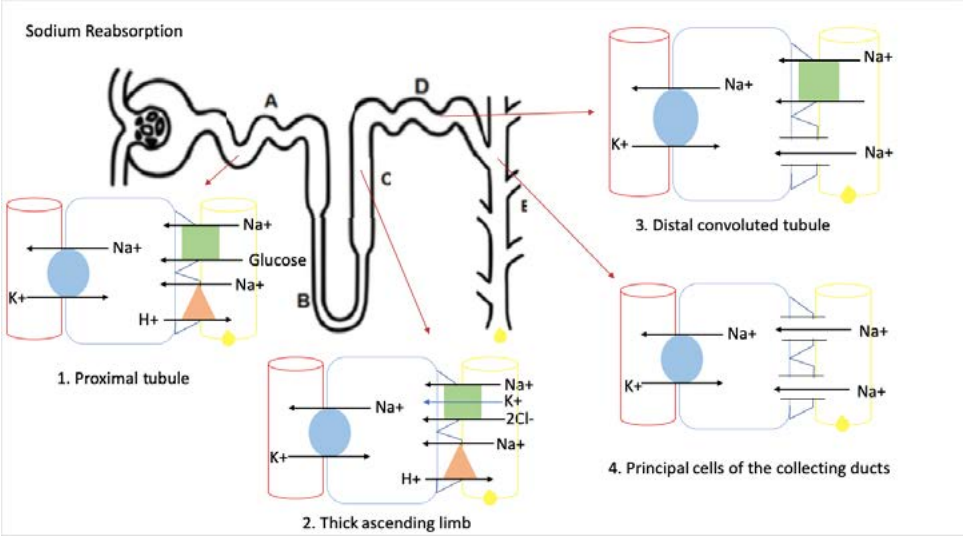

Figure 3: Sodium handling by the nephron

mechanisms depend on the Na/K ATPase, which reduces the concentration of sodium in the cell and maintains a negative intracellular potential. Three sodium ions are reabsorbed for every two potassium ions secreted using this ATPase. There is a constant amount of sodium and water reabsorption that occurs independent of the GFR due to oncotic pressure in the peritubular capillaries, otherwise, sodium reabsorption generally matches the GFR in this part of the tubule.[2,4,6]

Thick ascending limb of the loop of Henle

In this part of the tubule, once again a Na/K ATPase is creating a negative intracellular gradient allowing sodium to be transported from the tubular lumen across the luminal membrane via two mechanisms. The first is co-transport with potassium and chloride (Na/K/2Cl). The second is counter-transport with hydrogen ions.[2,4]

Distal convoluted tubule

Again, the Na/K ATPase pump is hard at work creating a negative intracellular environment. In this part of the tubule, sodium is reabsorbed from tubular fluid via special sodium-channels and also by co-transport with chloride.[2,4]

Collecting ducts

Sodium reabsorption in this part of the nephron involves the principal cells of the collecting ducts, which contain sodium-channels. Sodium moves down its concentration gradient once again due to the action of the Na/K ATPase located on the basal aspect of the cell.[2,4]

Ion exchange in the nephron: water reabsorption

The descending thin limb and the bend towards the ascending thick limb of the loop of Henle are freely permeable to water. Thereafter the thick ascending limb and the distal convoluted tubule are impermeable to water movement. The collecting duct is partially permeable to water through the action of ADH, which inserts aquaporins to enhance water reabsorption. Generally speaking, water will be reabsorbed with sodium creating an osmotic gradient between the tubular fluid and capillaries.[2]

Ion exchange in the nephron: chloride handling (Figure 4)

Chloride exchange in the nephron can occur via transcellular and paracellular mechanisms.

Thick ascending limb of the loop of Henle

We recall that chloride is reabsorbed in this part of the tubule along with sodium and potassium in a co-transporter system.[2]

Distal convoluted tubule

Chloride again moves with sodium from the tubular fluid into the cell with a co-transporter.[2]

Collecting ducts

Type B intercalated cells facilitate chloride movement here using a counter-transport mechanism with bicarbonate, which is dependent on the basal hydrogen ATPase. Chloride is then reabsorbed through chloride-specific channels.[2]

Ion exchange in the nephron: glucose handling

Proximal convoluted tubule

All of the glucose contained in the tubular fluid is reabsorbed in this part of the tubule. This is through co-transport with sodium, as previously discussed. If there is too much glucose in the tubular fluid the reabsorption capability of the tubule at this point is overwhelmed and glucose will begin to appear in the urine. This phenomenon is termed the transport maximum. At a normal GFR of 125 ml/min, glucose will appear in the urine at a threshold of about 10–12 mmol/l. Glucose transport mechanisms in this part of the tubule will be fully saturated at around 15 mmol/l, again if the GFR is normal.[2]

Ion exchange in the nephron: urea and protein reabsorption

Proximal convoluted tubule

This part of the tubule reabsorbs 50% of the urea load in the tubular fluid through passive diffusion.[2]

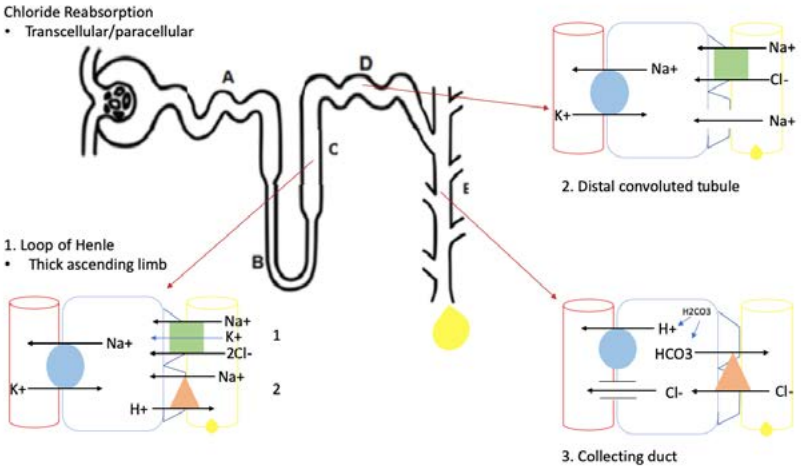

Figure 4: Chloride handling by the nephron

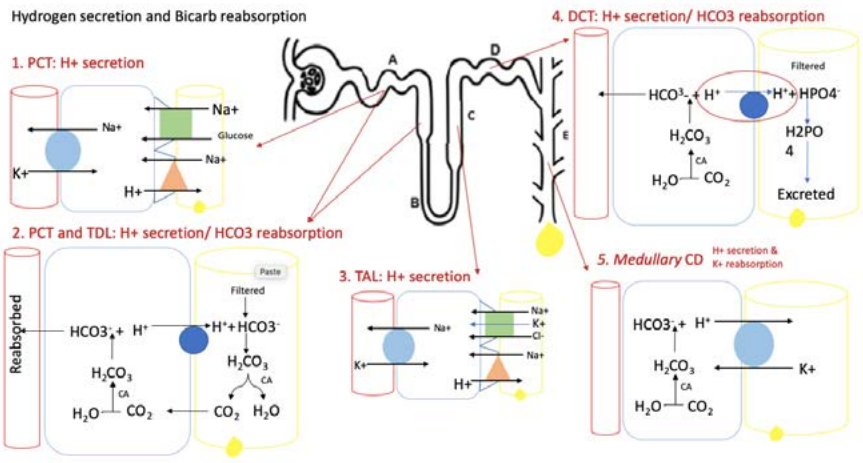

Figure 5: Hydrogen secretion and bicarbonate reabsorption

Medullary collecting ducts

Another 10% of the urea load is reabsorbed here. The permeability of this part of the nephron to urea is improved through the action of ADH.[2]

Proteins

The glomerular membrane is mostly impermeable to proteins, which are generally too large to cross the membrane. Some albumin does pass through the glomerulus and most of this load will be reabsorbed by the tubules. Large proteins are transported via endocytosis. There also exists a transport maximum for proteins and normal urine protein content averages about 100 mg per day.[2]

Ion exchange in the nephron: potassium handling

Thick ascending limb of the loop of Henle

Potassium is reabsorbed along with sodium in this part of the nephron with the help of a co-transporter along with chloride (Na/K/2Cl).[2]

Distal convoluted tubule and cortical collecting duct

Special type A cells reabsorb potassium into the blood in this part of the nephron whilst principal cells secrete potassium into the tubular fluid. The cortical collecting duct is an important area for potassium exchange compared with other parts of the nephron.[2]

Medullary collecting duct

This part of the tubule reabsorbs potassium but never secretes it. The net effect of these processes is that there is usually potassium that will appear in the urine, depending on intake. During states of potassium depletion, reabsorption will predominate.[2]

Ion exchange in the nephron: hydrogen secretion and bicarbonate reabsorption (Figure 5)

These processes occur in most parts of the nephron.

Proximal convoluted tubule

Using a counter-transport mechanism, hydrogen is secreted in exchange for sodium reabsorption. Bicarbonate is also reabsorbed in this part of the tubule with hydrogen secretion using a hydrogen transporter on the luminal edge of the cell. This reacts with filtered bicarbonate in the tubular fluid to generate carbonic acid, which then dissociates into carbon dioxide and water. The carbon dioxide diffuses back into the cell and combines with water in the cell to again form carbonic acid. Inside the cell, this reaction generates more hydrogen ions that are secreted and bicarbonate ions that are reabsorbed.[2]

Thick ascending limb of the loop of Henle

Hydrogen is secreted here into the tubular fluid in exchange for sodium ions, which are absorbed into the cell with a hydrogen-sodium (H/Na) counter-transporter.[2]

Distal convoluted tubule

Here hydrogen secretion into the tubular fluid uses a hydrogen transporter. In the tubular fluid, hydrogen reacts with hydrogen phosphate ions to produce phosphoric acid, which is excreted. Bicarbonate is generated in the cell via the reaction of carbon dioxide with water using carbonic anhydrase and is then reabsorbed.[2]

Medullary collecting ducts

A hydrogen-potassium (H/K) exchanger facilitates potassium reabsorption and hydrogen ion excretion.[2,4]

Countercurrents

Countercurrent multiplier

The countercurrent multiplier exists to create a tonic renal interstitium that increases in tonicity with increasing depth into the renal medulla. This mechanism occurs in the loop of Henle. It is made possible because the descending limb of the loop of Henle is impermeable to solute and permeable to water.

The ascending limb is impermeable to water and permeable to solute using the Na/K/2Cl co-transporter to pump out solute.[1,2,4,6]

Countercurrent exchanger: the vasa recta

Vasa recta is the name given to the capillaries in the renal medulla, which are also shaped in hairpin bends that are tucked into the loop of Henle. Flow in the vasa recta is in the opposite direction to the flow of fluid in the tubule. This allows the tonic gradient, which is generated by the loop of Henle with the countercurrent multiplier, to be maintained. If the vasa recta were linear, electrolytes would move in and out of the capillary and the tonicity of the interstitium would be lost.[1,2,4,6]

Conclusion

The renal function relies on a complex network of feedback mechanisms from the body regulating the GFR and allowing water and ions to be reabsorbed and excreted as needed to achieve homeostasis. Akin to the streets of a busy city, the movement of ions across cells in the nephron is complex and tightly regulated. A thorough understanding of these networks and ion movements is vital for all anaesthetists.

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References

1. Sherwood L. Human physiology: from cells to systems. 7th ed. Brooks Cole; 2010.
2. Kam P, Power I. Principles of physiology for the anaesthetist. 4th ed. CRC Press; 2020. https://doi.org/10.1201/9780429288210.
3. Atherton JC. Renal physiology. Br J Anaesth. 1972;44:236-45. https://doi.org/10.1093/bja/44.3.236.
4. Butterworth JF, Mackey DC, Wasnick JD. Morgan and Mikhail's clinical anesthesiology. 7th ed. United States: McGraw Hill; 2022.
5. Dewangan N. Nephron- definition, structure, physiology, functions. Microbe Notes; 2023. Available from: https://microbenotes.com/nephron-structure-functions/. Accessed 8 September 2023.
6. Gwinnutt M, Gwinnutt J. Renal physiology - part 2. World Federation of Societies of Anaesthesiologists; 2012.

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FCA REFRESHER COURSE

An applied pharmacokinetic approach to adjusted drug dosing: Part I – physiological states

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A patient's age, weight, gender, and pathophysiological state are some factors that may necessitate the adjustment of drug dosing. In addition, pharmacokinetics and pharmacogenomics, drug-drug and food-drug interactions may further alter the pharmacokinetics and pharmacodynamics of a drug. In part I of this topic, the basic principles of pharmacokinetics and the physiological factors that affect drug dosing viz. extremes of age and pregnancy are discussed.

Keywords: applied pharmacokinetics, adjusted drug dosing, physiological states

Introduction

The goal of any pharmacotherapeutic intervention is to achieve the desired clinical effect by reaching and maintaining an adequate effect-site concentration, using the minimum effective dose of a drug for a predictable amount of time.[1]

Dosing is prescribed according to the amount of drug per unit of time.[1] It must include the drug name, unit dose volume, route and frequency of administration, and length of treatment, e.g. cephazolin 1 g intravenously every 8 hours for 72 hours. Drugs may be prescribed as either a loading or a maintenance dose, with the main difference being that the loading dose is dependent on the volume of distribution (Vd), while maintenance doses are dependent on plasma clearance.[2,3] A loading dose is usually prescribed when a drug needs to reach a steady-state rapidly and it rarely needs to be modified.[3] In comparison, maintenance doses are used to maintain the steady-state plasma concentration and are dependent on patient physiological characteristics, and may therefore require dose adjustment.[3]

Drug dosage should be prescribed after careful consideration of both the patient and drug characteristics, and whether the need exists for adjustment from what would normally be prescribed. To appreciate the nuances of appropriate drug dosing, one needs a solid grasp of the fundamental principles of pharmacokinetics, as well as knowledge of individual drug pharmacology and patient pathologies.[4]

Basic principles of pharmacokinetics

Pharmacokinetics describe the factors that influence how a drug moves through the body from administration to elimination, and the resultant tissue drug concentrations over time.[5,6] The pharmacokinetic principles of absorption, distribution, metabolism, and excretion (ADME) apply.[7]

Drug absorption and bioavailability

Drug absorption influences the speed and concentration at which the drug reaches its effect site. It also includes liberation, which is the process where the drug is released to its active form.[5]

Bioavailability refers to the fraction of the administered drug that reaches the systemic circulation.[5] Drugs that are administered intravenously are 100% bioavailable, whereas drugs administered via other routes are subject to intra- and extrahepatic metabolism and excretion before reaching the systemic circulation.[2,5]

The area under the curve (AUC) method uses the plasma concentration over a given time to calculate the bioavailability of drugs with different distribution characteristics.[5] The integral of the curve is used to express the bioavailability of the substance in comparison to the 100% bioavailability of an intravenously administered substance.[5]

Distribution

Distribution refers to how the unmetabolised drug disperses between the intravascular (blood/plasma) and extravascular (intracellular and extracellular) compartments of the body and is dependent on the biochemical properties of the drug, as well as the physiology of the patient.[2,4,5,8]

Drugs have variable distribution patterns in different types of tissue based on their molecular structure and their binding abilities.[2,5] Drug distribution is influenced by various factors including tissue perfusion, tissue binding, lipid solubility, and plasma protein binding.[8] The goal is to reach an effective drug concentration at its designated compartmental destination, which is largely dependent on the Vd of the drug.[2]

Volume of distribution (Vd)

The Vd is the ratio of the total amount of the drug in the body to the drug concentration in the plasma at a given time.[2] It is useful in estimating the dose required to achieve a given plasma concentration.[6] Variations in Vd mainly affect the plasma concentration of the drug, which can directly impact the efficacy/toxicity of the drug.[2,8]

The following equation represents Vd:[2]

$$\text{Vd (L)} = \frac{\textbf{A(t)}\ \text{(mg) (Amount of drug in the body at time = t)}}{\textbf{C(t)}\ \text{(mg/L) (Plasma concentration of the drug at time = t)}}$$

Based on the above equation, a drug with a high Vd requires a higher dose to achieve the desired plasma concentration, as it tends to leave the plasma and enter the extravascular compartments of the body. The opposite is true for drugs with a low Vd.

Biochemical properties

The biochemical properties of a drug affect its distribution in the body.[2,5] These properties include the fat or water solubility (lipophilicity vs. hydrophilicity), polarity, and acidity or alkalinity of a drug.[2,5] Lipophilic drugs are more likely to have a higher Vd as they pass through lipid bilayers and distribute to areas with high lipid density, such as adipose. Hydrophilic molecules have a lower Vd as they are more likely to remain in the intravascular space.

Depending on its charge at physiological pH, a drug may bind macromolecules inside or outside the plasma.[5] Compared to neutral or basic molecules, acidic molecules have a higher affinity for albumin molecules at lower lipophilicity and are more likely to bind albumin and remain in the plasma, leading to a lower Vd.[2] Basic (alkaline) molecules have strong interactions with negatively charged phospholipid head groups located on phospholipid membranes; however, the overall lipophilicity of the drug will determine the extent of binding. In general, basic molecules will leave the systemic circulation leading to a higher Vd compared to acidic molecules.[2]

Plasma protein binding

Depending on its affinity for plasma proteins, a drug exists in equilibrium between a protein-bound or free form within each compartment of the body.[9] The greater the affinity, the greater the proportion of binding. If the protein binding is reversible, then a chemical equilibrium will exist between the bound and unbound states, such that protein + drug ⇌ protein-drug complex.[5,9] As the unbound fraction of the drug is metabolised and cleared, the bound fraction will then be released to maintain equilibrium. It is only the unbound fraction that exerts a pharmacological effect and that can undergo metabolism and elimination.[5] The bound fraction of the drug may act as a reservoir from which the drug is slowly released, thus influencing the drug's biological half-life.[5,9]

Acidic and neutral drugs primarily bind to albumin, which is alkalotic. Once albumin becomes saturated, these drugs then bind to lipoprotein. Basic drugs will bind to the acidic alpha-1-acid glycoprotein.[9] If plasma protein levels are low, the unbound fraction of the drug will be greater than expected and may potentiate the effects of the drug. The concentration of the drug in the body, the amount and quality of plasma proteins and their binding sites, and competition from other drugs that bind to plasma proteins all determine the unbound fraction of the drug.[2,5,9]

Hepatic clearance and metabolism

Hepatic metabolism is the major elimination pathway for most drugs.[10] The clearance of a drug in the liver is determined by hepatic blood flow and the hepatic extraction ratio (ER) of the drug.[10] Hepatic extraction is dependent on liver blood flow, the intrinsic clearance of the unbound drug, and the fraction of unbound drug in the blood [6,10] The ER refers to the proportion of hepatocyte uptake of the drug from the hepatic arterial circulation, subsequently making it available for metabolism.[6] Intrinsic hepatic clearance refers to the activity of enzymes and transporters involved in the elimination of drugs by metabolism and biliary excretion.[10] For high ER drugs (e.g. propofol and fentanyl), hepatic elimination is limited only by hepatic blood flow.[6] Conversely, hepatic clearance of low ER drugs (e.g. phenytoin and ceftriaxone) is limited by the intrinsic metabolic capacity of hepatocytes and the unbound fraction of the drug in plasma, and it remains relatively independent of hepatic blood flow. Drugs can be classified as having a high (> 0.7), intermediate (0.3–0.7), or low (< 0.3) ER, which is a function of the efficiency of the liver in removing the substance from circulation.[10]

The metabolism of drugs can occur in various reactions, categorised as phase I (modification), phase II (conjugation), and in some instances, phase III (additional modification and excretion).[11,12] Phase I modifications are made either by removing hydrogen or adding oxygen to more polar molecules. In some instances, this process changes an inactive prodrug into a metabolically active drug.[11,12] In phase II reactions, a drug molecule couples with another molecule in a conjugation reaction. Conjugation usually renders the compound pharmacologically inert and water-soluble, allowing the compound to be easily excreted.[11,12] A critical factor in the efficient metabolism of drugs is the enzymatic catalysis of phase I and II processes, which are heavily dependent on the concentrations of the various liver enzymes.[11]

Metabolism affects the plasma concentration of some drugs, and the reverse is also true. Certain drugs have an inhibitory effect on enzymes, increasing the patient's sensitivity to other medications metabolised through the action of those enzymes.[11] In contrast, enzyme induction may occur consequent to the repeated use of the same chemical. The body becomes tolerant of the drug and compensates by increasing the production of enzymes necessary for the drug's metabolism. This necessitates increasing doses to produce the same effect. Furthermore,

drugs that share elements of their metabolic pathways can also "compete" for the same binding sites on enzymes, decreasing their metabolism's efficiency.[11] Therefore, dose adjustments for drug-drug interactions should be taken into consideration.

Elimination and clearance

The kidneys are primarily responsible for the completion of the drug elimination process, which begins in the liver.[12] As lipophilic drugs readily cross the cell membrane of the kidney tubules and are reabsorbed into the blood, they first need to be metabolised in the liver before excretion of the drug becomes possible.[12] Polar drugs, or their metabolites, undergo glomerular filtration and typically do not undergo reabsorption before being excreted in the urine.[12] Urinary pH has a significant impact on drug ionisation and subsequent excretion (i.e. increased excretion occurs with weak acidic drugs in basic urine and weak basic drugs in acidic urine).[7]

Ionised drugs with a molecular weight > 300 g/mol are actively secreted by the liver into bile, which reaches the digestive tract and is either eliminated in faeces or reabsorbed as part of the enterohepatic cycle.[12] Excretion may also take place in the lungs, breast milk, sweat, saliva, and tears.[12]

Pharmacokinetic differences at the extremes of age

Body composition

Age and gender determine the patient's body composition (Table I).[7,13] At birth, the total body water (TBW) is at its highest, with term and preterm neonates having a TBW of 75% and 80%, respectively.[7] With increasing age, there is a progressive reduction in TBW and lean body mass, resulting in a relative increase in body fat.[13] The intracellular water remains relatively stable after the first month of life to adulthood.[7]

Table I: Average TBW composition according to age[7,13]

Age	Average TBW (as a % of weight)
Neonate	75–85
Toddler	70
Child	65
Adult male	60
Adult female	55
Geriatrics	50–55

Volume of distribution (Vd)

Hydrophilic versus lipophilic drugs: paediatrics

Younger children require higher doses of water-soluble drugs per kilogram weight because they have a higher percentage of TBW.[7] Lipophilic drugs have a relatively larger Vd in infants when compared to older children, due to a higher fat percentage (22.4% at 12 months *vs*. 13% at 15 years).[7]

Hydrophilic versus lipophilic drugs: geriatrics

With age-related changes in body composition, water-soluble drugs tend to have a lower Vd resulting in higher serum levels in older people.[13] Lipid-soluble drugs (notably diazepam, thiopentone, and lignocaine) have an increasing Vd with age, with the subsequent effect of a half-life prolongation.[13] Notably, the reduction in Vd for water-soluble drugs tends to be balanced by a reduction in renal clearance with little net effect on elimination half-life.[13]

Plasma protein binding: paediatrics

In newborns, total plasma protein concentrations are 86% of adult values.[7] The influence of plasma protein binding becomes significant in drugs that have a high degree of protein binding (> 95%) and is likely to be most pronounced in newborns and infants.[7] Table II shows a comparison of plasma protein composition binding in paediatric populations compared with adult reference values.[7]

Table II: Difference in plasma protein composition within the paediatric population

Parameter	Neonate	Infant	Child
Total protein	↓	↓	↔
Plasma albumin	↓	↔	↔
Plasma globulin	↓	↓	↔
alpha-1-acid glycoprotein	↓	N/A	↔
Free fatty acids	↑	↔	↔
Unconjugated bilirubin	↑	↔	↔

Plasma protein binding: geriatrics

In the older population, no substantial age-related changes in the concentrations of both these proteins have been observed. However, it should be considered that the geriatric population is at risk for malnutrition as well as recurrent illness. Albumin is commonly reduced in malnutrition or acute illness, whereas alpha-1-acid glycoprotein is increased.[13]

Metabolism

Paediatrics

The microsomal protein content within the liver increases with age from an estimated 26 mg/g in newborns, rising to a maximum of 40 mg/g in a 30-year-old adult. [7] Therefore, drugs that are highly metabolised are usually administered at a lower mg/kg^{-1} dose in newborns compared with preschool children.[7]

Infants and preschool children have a larger ratio of liver to total body mass, resulting in increased hepatic clearance of drugs as liver blood flow is increased compared with adults.[7,14] This can increase the first pass effect, but the overall metabolism is still subject to the level of enzyme activity.

Interestingly, there are differences in enzyme expression and activity that may result in the altered metabolism of drugs or the production of metabolites in paediatric populations that are not observed in adults Therefore, the ontogeny of specific metabolic pathways needs to be understood before extrapolating adult data onto paediatric populations.[14,15]

Geriatrics

There is an association of a reduction in liver mass and blood flow with increasing age, which will mainly affect first pass metabolism and the clearance of drugs with a high ER that are metabolised by phase I pathways in the liver.[13,16] The activity of drug-metabolising enzymes is usually preserved, and enzyme inhibition and conjugation pathways remain similar in young subjects.[13,16]

Elimination

Paediatrics

The elimination of drugs and their metabolites occurs predominantly via the kidneys. In term neonates, the glomerular filtration rate (GFR) is 2–4 ml/min/1.73 m^2, and it doubles by day seven, reaching adult values after the first year of life.[17,18] Newborns have a lower renal excretion of the unchanged drug due to renal immaturity, while infants and older children have a higher rate of renal clearance for some drugs due to a relatively larger kidney-to-body size.[18] The elimination of drugs can also be influenced by the origination and development of renal tubular transport mechanisms.[19]

Creatinine clearance is often used to estimate GFR in children; a reduction in drug dose is advised if creatinine clearance is less than the normal GFR.[19] Infant urinary pH is lower than adult values, which may increase the reabsorption of weak acidic drugs.[7]

Geriatrics

There is an age-associated reduction in renal function that may significantly affect not only renally excreted drugs but also drugs undergoing extensive metabolism in the liver.[13] In addition, polypharmacy is common in the elderly and can lead to an increase in side effects, drug interactions, adverse drug reactions, and non-adherence.[20] Together with alterations in other pharmacokinetic parameters, elderly patients are more susceptible to the side effects of drugs, viz. sedation, nephrotoxicity, hepatotoxicity, cardiotoxicity, confusion, dizziness, hypotension, and hypoglycaemia. There should therefore be an increased awareness about common drug interactions and whether prescribed drugs are inducers or inhibitors of the cytochrome (CYP) P450 enzymes.[20]

Pharmacokinetic changes in pregnancy

Body composition

During pregnancy, there is approximately a 42% increase in plasma volume, with parallel increases in TBW and all body fluid compartments.[21]

Volume of distribution (Vd)

This expanded extracellular volume and TBW increases the Vd for hydrophilic drugs.[6] Additionally, the increase in maternal body fat increases the Vd for lipophilic drugs, leading to overall lower plasma concentrations.[6]

There is an increase in uterine perfusion, and small molecular weight and lipophilic drugs readily cross the placenta. Additional compartments in the form of the foetus, placenta, and amniotic fluid can lead to increased drug accumulation and an apparent increase in Vd of certain drugs.[6]

Plasma protein binding

In pregnancy, there is a decreased plasma protein concentration of both albumin and alpha-1-acid glycoprotein, which can be clinically significant for certain drugs.[6] Where possible, it is safest to monitor free drug concentrations and adjust drug dosing to maintain the unbound drug concentration within its therapeutic range. A dose titration strategy aiming at maintaining therapeutic plasma concentrations can lead to increased free drug concentrations and increase the likelihood of drug-related toxicity.[6]

Metabolism

While the liver accounts for the metabolism of a vast majority of drugs, other organs including the intestine and placenta can also contribute to the clearance of certain drugs.[6] Metabolic enzyme activity in pregnancy is highly variable with maternal genotype, in addition to variations associated with ethnicity, gender, age, and certain disease states that are unrelated to pregnancy. Oxidative phase I reactions, which are predominantly carried out by the CYP450 enzymes, are significantly affected in pregnancy.[6] The activities of CYP3A4 (50–100%), CYP2A6 (54%), CYP2D6 (50%), and CYP2C9 (20%) are all increased.[6] In contrast, other CYP isoforms, like CYP1A2 and CYP2C19, demonstrate a gradual decrease in activity with advancing gestation. However, the effects of drug therapy remain uncertain.[6]

The activity of phase II enzymes, including uridine 5'-diphosphate glucuronosyltransferases (UGTs), is also altered during pregnancy with a 200% increase in UGT1A4 activity during the first and second trimesters, and a 300% increase during the third trimester.[6] This change leads to lower concentrations of UGT1A4 substrates such as lamotrigine, leading to subtherapeutic outcomes in the absence of appropriate dose titration.[6]

Elimination

In pregnancy, there is increased renal clearance of drugs that are solely excreted by glomerular filtration, as the GFR is 50% higher in the first trimester and continues to increase until the last week of pregnancy.[22] Despite a uniform increase in GFR during pregnancy, differences in renal tubular transport (secretion or reabsorption) can result in differing effects of various renally cleared drugs (e.g. lithium, digoxin, and atenolol), thereby limiting generalisation about the effect of pregnancy on renally eliminated drugs.[22]

Conclusion

Several physiological factors need to be considered when dosing a drug. Changes in pharmacokinetics may be non-linear in many cases. Therapeutic drug monitoring should be instituted where feasible, particularly in drugs with a narrow therapeutic index.

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References

1. Maheshwari R, Sharma PA, Seth A, et al. Drug disposition considerations in pharmaceutical product. In: Tekade RK, editor. Dosage form design considerations. Elsevier; 2018. p. 337-69. https://doi.org/10.1016/B978-0-12-814423-7.00010-1.
2. Mansoor A, Mahabadi N. Volume of distribution [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545280/. Accessed 26 September 2023.
3. Toutain PL, Bousquet-Mélou A. Volumes of distribution. J Vet Pharmacol Ther. 2004;27(6):441-53. https://doi.org/10.1111/j.1365-2885.2004.00602.x.
4. Powell JR, Cook J, Wang Y, Peck R, Weiner D. Drug dosing recommendations for all patients: a roadmap for change. Clin Pharmacol Ther. 2021;109(1):65-72. https://doi.org/10.1002/cpt.1923.
5. Grogan S, Preuss CV. Pharmacokinetics [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK557744/. Accessed 26 September 2023.
6. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol. 2015;39(7):512-9. https://doi.org/10.1053/j.semperi.2015.08.003.
7. Batchelor HK, Marriott JF. Paediatric pharmacokinetics: key considerations. Br J Clin Pharmacol. 2015;79(3):395-404. https://doi.org/10.1111/bcp.12267.
8. Onetto AJ, Sharif S. Drug distribution [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK567736/. Accessed 26 September 2023.
9. Scheife RT. Protein binding: what does it mean? DICP. 1989;23(7-8 Suppl):S27-31. https://doi.org/10.1177/106002808902300706.
10. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147-61. https://doi.org/10.1007/s00228-008-0553-z.
11. Susa ST, Hussain A, Preuss CV. Drug metabolism [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK442023/. Accessed 26 September 2023.
12. Garza AZ, Park SB, Kocz R. Drug elimination [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK547662/. Accessed 26 September 2023.
13. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2003;57(1):6-14. https://doi.org/10.1046/j.1365-2125.2003.02007.x.
14. Hines RN. The ontogeny of drug metabolism enzymes and implications for adverse drug events. Pharmacol Ther. 2008;118(2):250-67. https://doi.org/10.1016/j.pharmthera.2008.02.005.
15. Anantharaju A, Feller A, Chedid A. Aging liver. A review. Gerontology. 2002;48(6):343-53. https://doi.org/10.1159/000065506.
16. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging. 2001;18(11):837-51. https://doi.org/10.2165/00002512-200118110-00005.
17. Anderson BJ, Holford NHG. Understanding dosing: children are small adults, neonates are immature children. Arch Dis Child. 2013;98(9):737-44. https://doi.org/10.1136/archdischild-2013-303720.
18. Chen N, Aleksa K, Woodland C, Rieder M, Koren G. Ontogeny of drug elimination by the human kidney. Pediatr Nephrol. 2006;21(2):160-8. https://doi.org/10.1007/s00467-005-2105-4.
19. Schwartz GJ. Does kL/PCr estimate GFR, or does GFR determine k? Pediatr Nephrol. 1992;6(6):512-5. https://doi.org/10.1007/BF00866487.
20. Cantlay A, Glyn T, Barton N. Polypharmacy in the elderly. InnovAiT. 2016;9(2):69-77. https://doi.org/10.1177/1755738015614038.
21. Qasqas SA, McPherson C, Frishman WH, Elkayam U. Cardiovascular pharmacotherapeutic considerations during pregnancy and lactation. Cardiol Rev. 2004;12(4):201-21. https://doi.org/10.1097/01.crd.0000102420.62200.e1.
22. Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. Kidney Int. 1980;18(2):152-61. https://doi.org/10.1038/ki.1980.124.

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FCA REFRESHER COURSE

An applied pharmacokinetic approach to adjusted drug dosing: Part II – pathophysiological states

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In addition to age, gender, and pregnancy, pathophysiological states such as extremes of body weight, organ dysfunction, and critical illness with sepsis are factors that affect the pharmacokinetics of drugs, thereby necessitating an adjustment of drug dosing.[1-5]

Keywords: applied pharmacokinetics, adjusted drug dosing, pathophysiological states

Pharmacokinetics at extremes of body weight

In the normal-weight individual, the total body weight (TBW) comprises 20% fat weight (FW) and 80% lean body weight (LBW) or fat-free mass (FFM).[1] Extremes of body weight may result in altered physiology that affects the pharmacokinetics of a drug (Table I).[1,2]

Underweight/malnutrition

In the underweight or malnourished individual, FW accounts for a decreased proportion of TBW, and the LBW tends towards TBW.[1] Catabolic states, such as starvation, have several consequences that affect protein binding, drug distribution, and clearance.[1] Adipose tissue is lost first, followed by muscle and lean tissues.[1] There is a reduction in the synthesis and function of proteins and hepatic enzymes. Total body water increases gradually, resulting in oedema secondary to reduced intravascular oncotic pressure because of reduced protein synthesis.[1] The effect of this is multifold: there is a higher volume of distribution (Vd) for water-soluble drugs and a lower Vd for fat-soluble drugs. As a result of the reduced protein binding, there is an increase in the fraction of free drugs available for hepatic metabolism.[1]

There is a decrease in hepatic enzyme synthesis and function, which affects drugs with a low hepatic extraction ratio. The increased free drug concentration may exceed the capacity for hepatic metabolism, resulting in higher plasma concentrations, a delayed offset, or prolonged terminal elimination.[1]

Overweight/obesity

Body fat composition varies with age, gender, and genetics.[7] With increased TBW in the obese, there is a greater increase in FW compared to LBW.[1] The rate of drug distribution and elimination is proportional to the LBW, which mainly consists of muscle and vessel-rich organs or tissues. Blood flow to adipose tissues accounts for up to 5% of cardiac output compared with 22% to lean tissues, with a further decrease to 2% in obesity.[6] With increased body weight, total body water also increases, although, at extremes of obesity, the proportion of total body water is reduced because most of the excess weight is FW.[1,6]

FW is comprised of areas of high lipid density (e.g. poorly vascularised adipose tissue) in which lipophilic drugs are more likely to distribute.[1,2,6] Therefore, lipophilic drugs have a high Vd at steady-state. This is significant in critical care where prolonged, repeated administration of drugs like morphine, propofol, and midazolam can result in a prolonged duration of action.[1] Once the infusion is stopped, the plasma or effect-site concentration decreases, and the drug redistributes into plasma and its effect sites from fatty tissues, prolonging the clinical effect and delaying terminal elimination.[1,6] This is more evident in the obese where FW is higher.[1]

Dosing scalars in extremes of body weight

Depending on the biochemical characteristics of a drug (e.g. lipid solubility, Vd), using TBW sometimes fails to account for changes in compartment size, leading to either under- or

Table I: Pharmacokinetic changes at extremes of body weight[1]

Physiological variable	Change in obesity	Change in malnutrition	Pharmacokinetic consequence
Total body water	↑	↑	↑ Vd for water-soluble drugs
Fat mass	↑	↓	↑ dose in the obese due to ↑ Vd
LBW	↑	↓	↑ clearance in obese patients
Plasma proteins	↑	↓	↑ plasma protein binding in obese patients
Cardiac output	↑	↓	↑ clearance in obese patients

overdosing of the drug.[1] Using derived indices such as ideal body weight (IBW), which approximates compartment size, or adjusted body weight (ABW), which incorporates a correction factor for drug distribution is preferable, particularly where drug concentration is critical.[1,2] Males and females exhibit a difference in the distribution and metabolism of adipose tissue, therefore some measures account for differences in sex.[1,2,6]

Dose adjustment according to LBW correlates well with drug clearance, and using a measure of LBW is better in obesity as it assumes either a distribution to lean tissues only (IBW) or to some of the additional fatty mass (ABW) to account for drug lipid solubility.[1,2] The predicted normal weight (PNWT) considers height, weight, and sex and corrects for the additional adipose tissue.[1]

Overall, TBW is used for drugs with a wide therapeutic window (e.g. succinylcholine) where absolute plasma concentration is less important but simultaneously at risk of overdosing hydrophilic drugs and underdosing hydrophobic drugs.[1,2] The LBW is best suited to the dosing of hydrophilic drugs, and ABW is used for drugs with a narrow therapeutic window where the effects of lipid distribution may significantly affect toxicity (e.g. gentamicin).[1-3] Table II is a summary of the various dosing scalars and their clinical application, and Table III presents the recommended dosing scalars for commonly used drugs in anaesthesia.

Patients who are at the extremes of weight need to be considered holistically when assessing their pathophysiological status along with the pharmacokinetic implications thereof. This includes associated comorbidities and potentially severe physiological or metabolic derangements with organ dysfunction.

Adjusted drug dosing in hepatic dysfunction and failure

Absorption and bioavailability

Patients with liver disease may present with alterations in drug absorption and bioavailability.[9,10] The decreased secretion of bile may result in malabsorption. Oral drug bioavailability may be increased in patients with portal venous hypertension as portosystemic shunts lead to a decrease in first pass metabolism.[9,11]

Distribution

Cirrhotic liver disease may result in the reduced protein binding of certain drugs due to the reduced hepatic synthesis and quality of plasma proteins viz. albumin and alpha-1-acid glycoprotein.[9] Moreover, the accumulation of endogenous compounds, such as bilirubin, may further inhibit the plasma protein binding of certain drugs with competition for binding sites.[9] Additionally, patients with ascites will have a higher Vd of water-solubility, necessitating larger loading doses.[10,12]

Biotransformation and elimination

Not all liver diseases have the same pharmacokinetic consequences affecting the hepatic biotransformation and

Table II: Formulae for weight-based calculations[1]

Term	Derivation	Explanation	Use	Caution
TBW (kg)	LBW + FW	As measured, includes both fat and lean weight	Dosing of many drugs most appropriate in the non-obese (where TBW tends to LBW) Succinylcholine, total intravenous anaesthesia (TIVA) maintenance (accounts for larger compartment size)	May lead to overdose if used in the obese population TIVA boluses by TBW may exaggerate haemodynamic effects
LBW (kg)	1.1 × TBW - 0.0128 × body mass index (BMI) × TBW (male) 1.07 × TBW - 0.0148 × BMI × TBW (female)	LBW comprised of non-adipose tissues	Useful for polar drugs with a small Vd, such as neuromuscular blocking agents, topical calcineurin inhibitors (bolus induction, avoids overdosing and instability)	Several formulae for calculation, and may be complex Error-prone, particularly at extremes of weight, depending on the formula used Not possible to measure directly in clinical practice
IBW (kg)	22 × height^2 (m)	The weight of an individual based on height and assuming a normal BMI of 22 kg/m^2	Recommended for calculation of local anaesthetic maximum doses	Assumes 15% body fat, which is not "normal" across all age ranges
ABW (kg)	LBW + C × (TBW - LBW) (where C is a drug-specific correction based on the solubility of the drug)	Assumes drug distribution to lean tissues and a proportion of the FW depending on the physiochemical properties of the drug	Dosing of drugs with a narrow therapeutic index (e.g. gentamicin)	Requires calculation using a correction factor specific to every drug Uses LBW (which may be error-prone, depending on the formula used)
PNWT (kg)	1.57 × weight - 0.0183 × BMI × WT - 10.5 (male) 1.75 × weight - 0.0242 × BMI × WT - 12.6 (female)	Consists of lean and fatty weight, corrected for the non-obese individual, an extension of IBW	Developed to overcome limitations of scaling to LBW or TBW	Specifically derived for drug dosing (rather than the classification of obesity) Not validated or in widespread clinical use currently

Table III: Dosing scalars for drugs commonly used in anaesthesia[1-3,8]

Drug	Recommended dosing scaler	Notes
Opioids		
Morphine	LBW	Highly lipophilic with a relatively large Vd. The increased sensitivity to opioids risks apnoea when dosed according to TBW. Caution in obstructive sleep apnoea. Cautious titration is recommended due to the variability of clinical effects.
Fentanyl & sufentanil	LBW	Rapid initial offset because of redistribution, with increased clearance in the obese. Caution of increased sensitivity to opioids. Cautious titration is recommended due to the variability of clinical effects.
Remifentanil	LBW	Significantly greater plasma concentrations when dosed by TBW rather than LBW, risking bradycardia. Cautious titration is recommended due to the variability of clinical effects.
Alfentanil	ABW	No data available. Manufacturer suggests LBW.
Anaesthetic induction agents		
Propofol	Initial bolus: LBW Infusion: TBW	Highly lipophilic with rapid redistribution. Initial bolus dosing by TBW may result in haemodynamic instability, but dosing by LBW risks awareness. Practically, dose boluses by LBW, and infusions by TBW.
Thiopental	Initial bolus: LBW Infusion: TBW	Dosed based on the same principles as propofol with risks of awareness after a bolus dose.
Etomidate	LBW	No data available; recommendation based on pharmacokinetic similarities to propofol.
Neuromuscular blockers and reversal agents		
Succinylcholine	TBW	Increase in pseudocholinesterase activity in the obese, resulting in relatively increased metabolism of succinylcholine. Dosing by TBW is appropriate without any associated adverse effects.
Atracurium & rocuronium	LBW	Polar, charged molecules with a small Vd; dose by calculated LBW. Dosing according to TBW results in a prolonged duration of action with no improvement in onset time for rocuronium.
Reversal agents		
Sugammadex	TBW/ABW	Few studies of sugammadex in the obese. Recommend titration to effect. The manufacturer recommends dosing by TBW.
Neostigmine & glycopyrrolate	TBW/ABW	Recommend titration to effect.
Local anaesthetics		
Lidocaine Bupivacaine	LBW IBW	Overall maximal dose calculated using standard limits based on LBW. The absolute maximum dose depends on the route of administration.
Prilocaine Ropivacaine	LBW IBW	

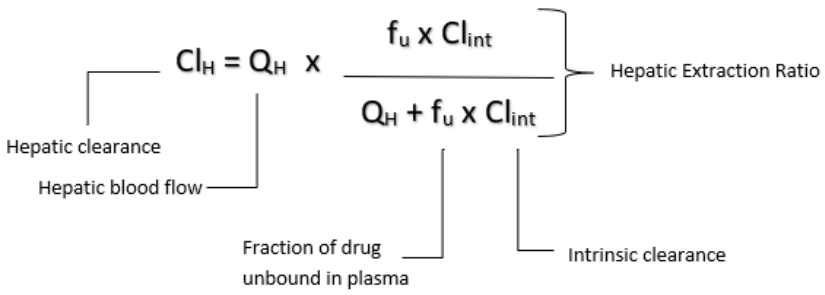

Figure 1: Determinants of hepatic clearance

clearance of drugs (i.e. the impairment of drug disposition has a strict correlation with the type and severity of liver disease).[9] Notably, the hepatic drug clearance in patients with liver cirrhosis is markedly decreased, whereas the metabolic function of the liver is usually maintained in patients with chronic hepatitis without cirrhosis, or with primary or secondary cancer.[9,11] Severe liver dysfunction is generally considered as albumin < 30 g/L, international normalised ratio > 1.2, and Child-Pugh class C.[11]

Importantly, there is no linear correlation between the hepatic metabolising capacity and biomarkers of liver function.[9,11]

Hepatic clearance is determined by hepatic blood flow and hepatic extraction ratio, which in turn is determined by the free drug in plasma and the intrinsic clearance (Figure 1).[13,14]

Intrinsic clearance is the ability of the liver to metabolise the drug without the restrictions of hepatic blood flow or protein binding. It is solely dependent on the activity of sinusoidal and canalicular transporters and hepatocyte metabolic enzymes.[9]

In patients with cirrhosis with increased disease severity, there is a proportional decrease in the concentrations of drug-binding proteins (especially albumin), as well as in the content and activity of phase I hepatic microsomal enzymes.[12] Notably, however, cirrhosis results in a variable and non-uniform

reduction in hepatic enzyme metabolic potential.[9,11] There is a greater decrease in the liver content of the phase I oxidising cytochrome (CYP) P450 enzymes with a resultant decrease in the clearance of drugs metabolised by CYP3A4/3A5, such as midazolam, in comparison to phase II conjugation reactions, such as glucuronidation.[9-12]

Data suggest that if the drug is a high clearance drug (liver blood flow dependent), a 50% reduction in dose is recommended, although there seems to be little difference in the metabolic clearances of both highly and poorly extracted drugs in cirrhotic patients.[11,12]

Elimination

Drugs with < 20% hepatic elimination and those that are mainly renally excreted are less likely to be affected by liver disease.[9] Drugs and metabolites that rely on biliary excretion will be retained and may require dose adjustment. Drugs that undergo enterohepatic recirculation may have decreased half-lives due to the failure of recirculation.[9,10]

Pharmacodynamic changes

Patients with decompensated liver failure may have altered tissue sensitivity to drugs.[3,9,11,12] For many drugs, both the drug and the metabolite(s) contribute to the overall therapeutic response of the patient to the drug. Therefore, the effect on the concentration of the active drug and the metabolite in the body should be known. A decrease in hepatic metabolism can result in a change in the potency of a drug; depending on whether the drug or its metabolite is more potent.[11] If a drug is more potent than its metabolite, the overall pharmacological activity will increase as the drug concentration will be higher. If the metabolite is more potent than the drug, the pharmacological effect of the drug will be decreased as less of the active metabolite is formed. Hepatic disease may result in complex pharmacological outcomes as the disease process itself has the potential to affect both the pharmacokinetics and pharmacodynamics of a drug.[3]

Extreme caution is recommended when using drugs with a narrow therapeutic index in patients with liver disease and when administering any drug to patients with severe liver dysfunction (Child-Pugh class C).[12] Drugs with a wide therapeutic range will be less affected by moderate hepatic dysfunction.[11]

There is an increased sensitivity to central nervous system depressants. The recommendations are to either avoid or reduce the dose of barbiturates, benzodiazepines, and opioids. Short-acting drugs that are reversible are preferable.[11]

In comparison to impaired renal function, the dose adjustment for impaired liver function, such as in patients with liver cirrhosis, is more complex because there is no single marker that can be used to adjust the dose.[11] The information on individual drug dose adjustment in patients with liver cirrhosis should ideally be found on the drug label or in published clinical studies.

Adjusted drug dosing in renal impairment and failure

Kidney disease can result in pharmacokinetic derangements of both the renal- and non-renal drug clearance, Vd, and bioavailability of drugs.[15] Renal impairment may lead to drug accumulation and potential toxicity by modifying the effects of many medications. Many of these alterations can and should be predicted and subsequently alleviated by adjusting drug doses, particularly in patients with chronic kidney disease (CKD).[15,16]

CKD (Table IV) is a pathology of gradual loss of kidney function occurring over a period of months to years and is characterised by the presence of both glomerular filtration rate (GFR) < 60 ml/min and albumin > 30 mg/g of creatinine, together with structural or functional abnormalities of the kidney for longer than three months. End-stage renal disease is defined as a GFR < 15 ml/min.[17] Therefore, the pharmacokinetic impact of the renal dysfunction should first be quantified according to the patient's actual GFR.[3,16]

Table IV: Stages of CKD

CKD stage	GFR (ml/min)	Renal insufficiency
1	120–90	Nil
2	89–60	Mild
3a	59–45	Intermediate
3b	44–30	Moderate
4	29–15	Severe
5	14–0	End stage; needs renal replacement therapy

The Cockroft-Gault formula (1973)

Historically, the Cockcroft-Gault equation was used as a measure of creatinine clearance; however, the use of this biomarker may lead to an underestimation of renal impairment, specifically among the elderly.[16,17] Furthermore, the Cockcroft-Gault equation relies on TBW and so overestimates the GFR in patients with obesity.[16,18]

GFR = {[(140–age) × weight] / (72 × creatinine)} × 0.85 [if female]

MDRD equation

The MDRD (Modification of Diet in Renal Disease) formula is now routinely reported on and indexes the GFR based on a normalised body surface area (i.e. ml/min/1.73 m^2). Conversion of MDRD-estimated GFR to non-normalised body surface area overestimates the GFR in patients with obesity.[16,18]

186 × (creatinine / 88.4) × (age) × 0.742 [if female, but × 1.210 if black]

CKD-EPI equation

A newer formula, CKD-EPI (named after the Chronic Kidney Disease Epidemiology Collaborative), has been adapted for research purposes.[19]

GFR = 141 × min (S/κ, 1) × max (S/κ, 1) × 0.993 × 1.018 [if female, but × 1.159 if black]

Abbreviations/units: S = serum creatinine in mg/dL, κ = 0.7 for females and 0.9 for males, α = -0.329 for females and -0.411 for males, min = the minimum of S/κ or 1, and max = maximum of S/κ or 1.

Understanding the concentration-time profile of a drug

The concentration-time profile approximates the clinical effect of most drugs, and drug exposure relates to the maximum plasma concentration (C_{max}) and/or the area under the concentration-time curve (AUC).[15] In general, high drug exposures increase the risk of adverse drug reactions, and low drug exposures are subtherapeutic.

In kidney disease, failure to appropriately adjust dosing may result in sub- or supratherapeutic dosing.[16,17] Subtherapeutic dosing may lead to treatment failure or drug resistance, while supratherapeutic exposure to drugs and their metabolites may result in systemic toxicity.[16,17] Increased renal clearance leads to lower drug concentrations and decreased clearance results in greater drug effects.

When the changes in pharmacokinetics due to kidney disease and other conditions are understood, the dosing regimen can be adjusted so that the concentration-time profile is optimised for the individual.[3,15] To avoid harm, the dose of renally cleared drugs should be decreased equivalent to the calculated reduction of drug clearance. The adjustments can be made in the following ways:[20]

- Constant interval: dose reduction method.
- Constant dose: interval extension method.
- By administering a loading dose at the start of the treatment.
- By monitoring the concentrations of drugs that have a narrow therapeutic index.

Changes in either the Vd or clearance have differing effects on the concentration-time profile.[15] Although a doubling in the Vd and a halving of clearance have the same effect on the elimination half-life, their concentration-time profiles are different. When clearance is halved, the AUC is doubled. When the Vd is doubled, the C_{max} is reduced, but there is no change to AUC despite the change in the concentration-time profile. In patients with altered kinetics, continuous dosing will lead to drug accumulation if the regimen is not adjusted.[15-17] Onset of toxicity will occur earlier from a decrease in clearance. Increasing the dosing interval will prevent drug accumulation, although where Vd is doubled, the C_{max} and average concentration will be lower than in an individual with normal kinetics, and the dosing regimen might be subtherapeutic.[15]

Table V: Recommendations for drug dosing in patients with hepatic and renal insufficiency[6,9-11]

Drug	Problem	Suggested action
Alfentanil	CL decreased by 50% t1/2β is prolonged Reduced protein binding	Reduce dose in patients with severe liver disease
Codeine	Metabolised to morphine CYP2D6, ceiling effect	Serum levels unpredictable Do not use for analgesia
Fentanyl	Pharmacokinetics of a single intravenous dose remain unaltered	A normal single dose can be used Prolonged recovery time after termination of continuous infusion
Hydrocodone	Metabolised to hydromorphone	As above
Hydromorphone	Reduced hepatic glucuronidation leads to an increase in oral bioavailability, decreased CL & prolonged t1/2β	Dose reduction Safe in renal impairment
Meperidine	Increased bioavailability of CNS active metabolite in renal and hepatic impairment with prolonged t1/2β	Avoid in patients with hepatic/renal impairment
Methadone	Prolongation of t1/2β & increase of Vd in patients with severe hepatic dysfunction Chronic alcohol abuse may increase methadone metabolism	A normal dose can be used in mild to moderate liver diseases Accumulation may occur in severe liver dysfunction
Morphine	Reduced hepatic glucuronidation leads to an increase in oral bioavailability, decreased CL & prolonged t1/2β in oral dose	Use with care in patients with severe liver cirrhosis Reduce the oral dose Metabolites increase toxicity in patients with renal failure
Oxycodone	Multiple metabolite levels are unpredictable	Reduce dose and frequency in renal impairment
Remifentanil	Pharmacokinetics unaltered	A normal dose can be used
Sufentanil	Pharmacokinetics altered & reduced protein binding with alkalosis associated with an increased Vd & t1/2β	A normal dose can be used Use with care when plasma pH is elevated
Tramadol	Reduced metabolism t1/2β of tramadol & O-desmethyltramadol approximately doubled	Prefer alternative analgesic; reduce dose frequency in patients with liver and renal impairment

CL – clearance, CNS – central nervous system, t1/2β – terminal elimination half-life, Vd – volume of distribution

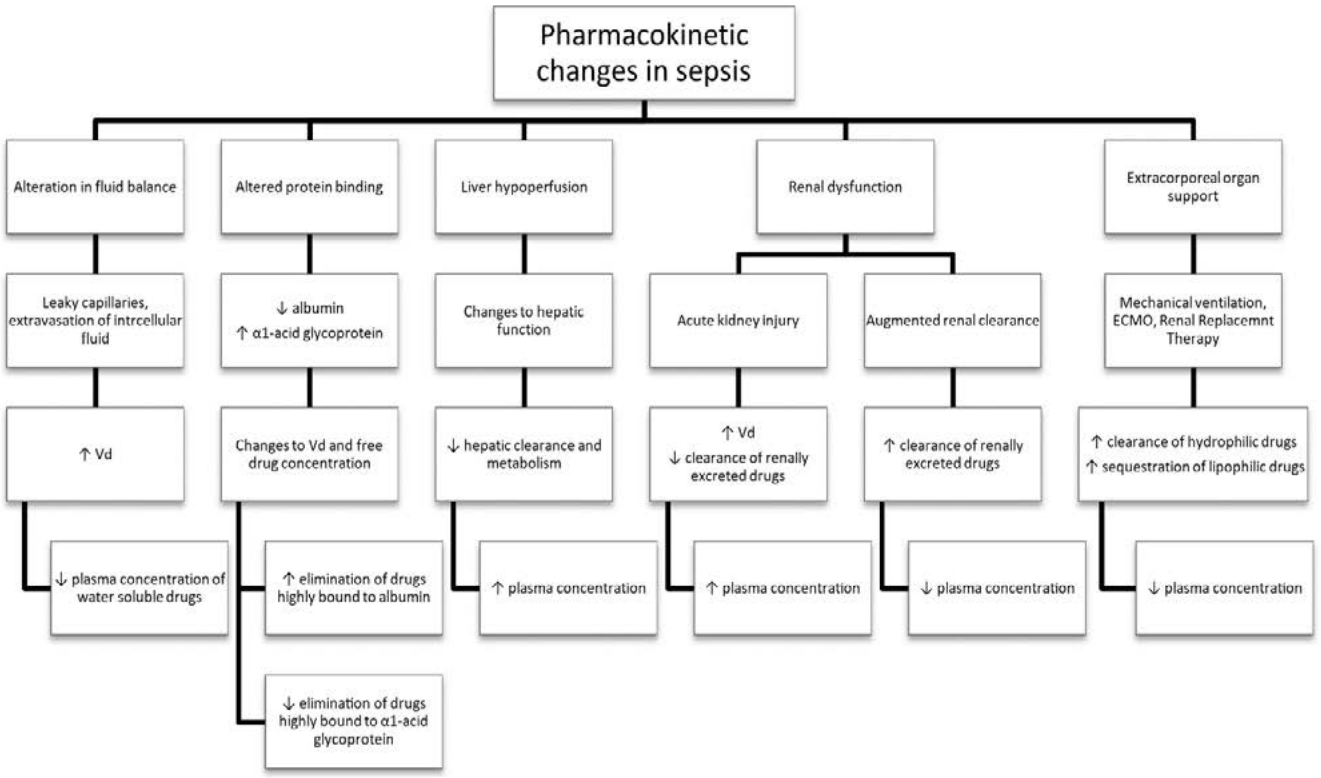

Figure 2: Pharmacokinetic changes in sepsis

Often, dose adjustments are crudely made in terms of halving the dose or doubling the dosing interval. Despite this, minor changes in dose or the concentration of drugs with a narrow therapeutic index may result in significant adverse effects.[15] Therefore, drug dosing should be optimised on a case-by-case basis using rational dose design grounded in an understanding of basic pharmacokinetic concepts along with therapeutic drug monitoring, particularly for drugs that have a narrow therapeutic index. This should be guided by knowledge of individual drug pharmacology and advice from the drug manufacturer, usually included in the package insert (Table V).

Pharmacokinetic implications in critically ill patients with sepsis

Critically ill patients pose a challenge to optimal drug dosing due to a plethora of haemodynamic, metabolic, and biochemical derangements (Figure 2).[5] These derangements can affect various pharmacokinetic processes, including drug absorption, distribution, metabolism, and elimination to differing degrees.

Absorption and bioavailability

In shock, blood flow is preferentially shunted to vital organs, including the brain and heart, whereas flow to other organs, including the gastrointestinal tract or subcutaneous tissue, may be reduced.[5] As a result, drug absorption may be altered in a haemodynamically compromised patient (with hypotension and shock) when administered via the gastrointestinal tract or subcutaneously. Intravenously administered drugs are recommended during the acute phase of sepsis or septic shock to avoid these concerns.[5]

Distribution

Several factors may influence the Vd in a critically ill patient.[5] Aggressive fluid resuscitation in response to hypotension and/or third spacing leads to an increase in the Vd, which in turn decreases plasma drug concentrations with standard dosing.[4,5] Hypoalbuminaemia is common in critically ill patients and may lead to an increase in both the Vd and elimination of unbound acidic antimicrobials. In addition, there may be increased expression of alpha-1-acid glycoprotein, an acute-phase reactant that binds to basic drugs, thereby decreasing their free drug concentrations.[4,5]

Metabolism and elimination

In sepsis or septic shock, hypoperfusion may lead to "shock liver" and significant hepatic dysfunction.[5] This may lead to alterations in hepatic enzyme activity and hepatic blood flow, which influence drug metabolism and clearance respectively.[4,5] The use of inotropes and vasodilators will increase portal and hepatic blood flow, while vasopressors induce the opposite effect by alpha-adrenergic-mediated vasoconstriction and consequent reduction of blood flow.[5]

Acute kidney injury (AKI) is common in critically ill patients. Renal clearance of hydrophilic drugs decreases with a decline in the GFR, potentially requiring dose adjustment depending on the degree of renal impairment. However, the need for increased loading doses in the setting of increased Vd should also be considered.[4,5] Furthermore, in some patients interventions like aggressive fluid resuscitation and the use of vasopressors can lead to an early increase in cardiac output and enhanced

renal blood flow, resulting in augmented renal clearance (ARC) defined as a GFR of ≥ 130 ml/min.[5] Patients with ARC may require dose modifications to avoid suboptimal antimicrobial exposure.

In patients undergoing renal replacement therapy, the drug clearance across a haemodiafilter membrane depends on the molecular weight and protein binding of the drug.[21] The larger the molecular weight, the less the filtration. Because blood proteins are too large to be cleared by the membrane, they will remain in the blood together with highly protein-bound drugs. The effluent (dialysate + ultrafiltrate) rate determines the drug clearance during dialysis. The faster the affluent rate, the greater the drug removal.[21]

The physiological alterations that affect drug pharmacokinetics pose a significant challenge in the management of critically ill patients. Standard dosing strategies are unlikely to consistently achieve therapeutic targets, which can lead to an increased risk of both clinical failure and the development of antimicrobial resistance.[4] The adjustment of dosing strategies with the use of loading doses or continuous infusions may be beneficial. Where possible, using an individualised dosing approach with therapeutic drug monitoring would be advantageous, considering the significant interpatient variability, especially in antimicrobial concentrations.[4,5] Pharmacotherapy targeted at therapeutic goals and therapeutic drug monitoring is currently the best option for the safe care of the critically ill.[4]

Conclusion

While this article by no means serves as a comprehensive formulary for adjustments in drug dosing, the author hopes that it stimulates thought on the physiological and pathophysiological processes that influence how drugs should be dosed and prescribed. Thorough background knowledge of individual drug pharmacology and disease processes is imperative and cannot be overemphasised.

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References

1. Hebbes CP, Thompson JP. Pharmacokinetics of anaesthetic drugs at extremes of body weight. BJA Educ. 2018;18(12):364-70. https://doi.org/10.1016/j.bjae.2018.09.001.
2. Ingrande J, Lemmens HJM. Dose adjustment of anaesthetics in the morbidly obese. Br J Anaesth. 2010;105(Suppl 1):I16-23. https://doi.org/10.1093/bja/aeq312.
3. Shargel L, Wu-Pong S, Yu ABC. Chapter 21. Dose adjustment in renal and hepatic disease [Internet]. In: Applied biopharmaceutics & pharmacokinetics. 6th ed. New York: The McGraw-Hill Companies; 2012. Available from: accesspharmacy.mhmedical.com/content.aspx?aid=56607716. Accessed 20 September 2023.
4. Gorham J, Taccone FS, Hites M. Ensuring target concentrations of antibiotics in critically ill patients through dose adjustment. Expert Opin Drug Metab Toxicol. 2022;18(3):177-87. https://doi.org/10.1080/17425255.2022.2056012.
5. Castro DM, Dresser L, Granton J, Fan E. Pharmacokinetic alterations associated with critical illness. Clin Pharmacokinet. 2023;62(2):209-20. https://doi.org/10.1007/s40262-023-01213-x.
6. Cheymol G. Effects of obesity on pharmacokinetics: implications for drug therapy. Clin Pharmacokinet. 2000;39(3):215-31. https://doi.org/10.2165/00003088-200039030-00004.
7. Campos I, Kotanko P. Chapter 157 - assessment of fluid status and body composition and control of fluid balance with intermittent hemodialysis in the critically ill patient. In: Ronco C, Bellomo R, Kellum JA, Ricci Z, editors. Critical care nephrology. 3rd ed. Elsevier; 2019. p. 956-60.e2. https://doi.org/10.1016/B978-0-323-44942-7.00157-6.
8. Members of the Working Party, Nightingale CE, Margarson MP, et al. Peri-operative management of the obese surgical patient 2015: Association of Anaesthetists of Great Britain and Ireland Society for Obesity and Bariatric Anaesthesia. Anaesthesia. 2015;70(7):859-76. https://doi.org/10.1111/anae.13101.
9. Susla GM, Lertora JJL. Chapter 7 - effect of liver disease on pharmacokinetics. In: Atkinson Jr AJ, Huang S-M, Lertora JJL, Markey SP, editors. Principles of clinical pharmacology. 3rd ed. Elsevier; 2012. p. 81-96. https://doi.org/10.1016/B978-0-12-385471-1.00007-6.
10. Tegeder I, Lötsch J, Geisslinger G. Pharmacokinetics of opioids in liver disease. Clini Pharmacokinet. 1999;37(1):17-40. https://doi.org/10.2165/00003088-199937010-00002.
11. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol. 2008;64(12):1147-61. https://doi.org/10.1007/s00228-008-0553-z.
12. Ozbey AC, Bachmann F, Duthaler U, et al. Dose adjustment in patients with liver cirrhosis - comparison of two different modeling approaches. Clin Pharmacol Ther. 2023;113(6):1346-58. https://doi.org/10.1002/cpt.2897.
13. Schmucker DL. Liver function and phase I drug metabolism in the elderly: a paradox. Drugs Aging. 2001;18(11):837-51. https://doi.org/10.2165/00002512-200118110-00005.
14. Susa ST, Hussain A, Preuss CV. Drug metabolism [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: http://www.ncbi.nlm.nih.gov/books/NBK442023/. Accessed 26 September 2023.
15. Lea-Henry TN, Carland JE, Stocker SL, Sevastos J, Roberts DM. Clinical pharmacokinetics in kidney disease: fundamental principles. Clin J Am Soc Nephrol. 2018;13(7):1085-95. https://doi.org/10.2215/CJN.00340118.
16. Kyriakopoulos C, Gupta V. Renal failure drug dose adjustments [Internet]. Treasure Island: StatPearls Publishing; 2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560512/. Accessed 26 September 2023.
17. Munar MY, Singh H. Drug dosing adjustments in patients with chronic kidney disease. Am Fam Physician. 2007;75(10):1487-96.
18. Michels WM, Grootendorst DC, Verduijn M, et al. Performance of the Cockcroft-Gault, MDRD, and new CKD-EPI formulas in relation to GFR, age, and body size. Clin J Am Soc Nephrol. 2010;5(6):1003-9. https://doi.org/10.2215/CJN.06870909.
19. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
20. Choudhary D, Goykar H, Kalyane D, Desai N, Tekade RK. Chapter 3 - dose, dosage regimen, and dose adjustment in organ failure. In: Tekade RK, editor. Biopharmaceutics and pharmacokinetics considerations: volume 1 in advances in pharmaceutical product development and research. Elsevier; 2021. p. 29-82. https://doi.org/10.1016/B978-0-12-814425-1.00004-8.
21. Jang SM, Infante S, Pour AA. Drug dosing considerations in critically ill patients receiving continuous renal replacement therapy. Pharmacy (Basel). 2020;8(1):18. https://doi.org/10.3390/pharmacy8010018.

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FCA REFRESHER COURSE

An approach to arterial blood gas analysis

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Keywords: balanced acid-base status, arterial blood gas

Introduction

A balanced acid-base status is critical for regular cellular and organ function and the survival of an organism. An arterial blood gas (ABG) machine is an accessible bedside tool of measurement, accessing both respiratory and metabolic disorders. Correct sampling, avoidance of common analytical errors, and correct interpretation of results are critical in guiding the administration of appropriate therapy. The adage "never do the test if you are not sure what to do with the results" is relevant concerning ABG analysis.

Historically and traditionally, the lungs and the kidneys have been considered important organs regulating acid-base balance. Next to these organs, the liver is now recognised as an important contributor to acid-base homeostasis. Understanding the collaboration, metabolic communication, and physiological interactions of these organs is crucial in understanding any acid-base derangement. These organs are the most important effectors, normalising the acid-base status.

An excess of metabolic acid is converted to volatile acid (CO_2) by the respiratory metabolic link and excreted by the lungs. Likewise, an excess of volatile acid is converted to metabolic acid and excreted by the kidney. This system is non-saturable. The hepatorenal link regulates the amount of bicarbonate generated or consumed, based on the alkalinity or acidity of arterial blood.

Physiological roles of organs in acid-base regulation

Lungs

Peripheral receptors, located in the aortic arch and carotid body, respond to acute changes in the arterial partial pressure of carbon dioxide ($PaCO_2$) and partial pressure of oxygen (PaO_2). In addition, carotid body chemoreceptors are sensitive to acute arterial blood pH changes.

Central chemoreceptors residing in the medulla are sensitive to acute changes in pH (H^+) in the extracellular fluid in the brain. These receptors also receive afferent input from the periphery via glossopharyngeal and vagus nerves. Central sensors linked to the respiratory centre, when activated, generate feedback

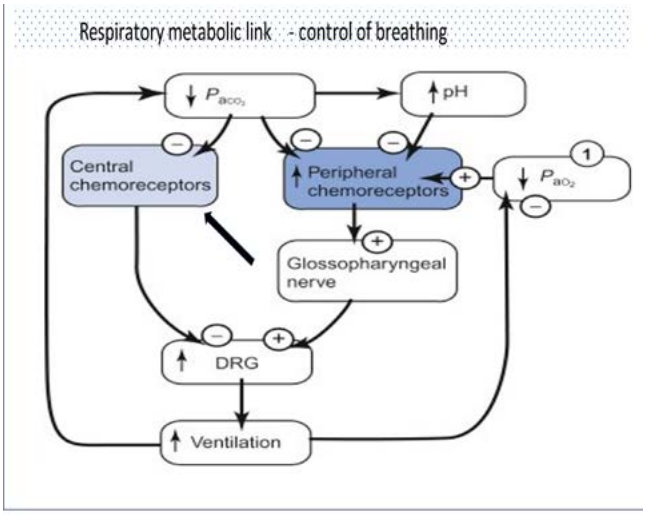

Figure 1: Chemical control of breathing and feedback loops. (DRG dorsal respiratory group)

mechanisms (negative or positive) to alter the respiratory pattern (Figure 1).

Cerebrospinal fluid (CSF) lacks the buffering capacity as little protein exists in the fluid. Therefore, a slight change in CSF PCO_2 results in a dramatic change in pH. Central correction is more rapid and effective than peripheral correction.

Liver

Lactate metabolism

Humans generate about 0.8 mmol/kg/hour of lactate and the healthy liver is the main consumer of lactate. About 30–70% of lactate is metabolised in the liver. It is converted to pyruvate and retransformed to glucose.

Albumin synthesis

In physiological pH, albumin behaves as a weak non-volatile acid. Its histidine residue donates a proton in a solution. Hypoalbuminemia represents a lack of acid and results in metabolic alkalosis hence base excess (BE) should always be corrected for albumin.

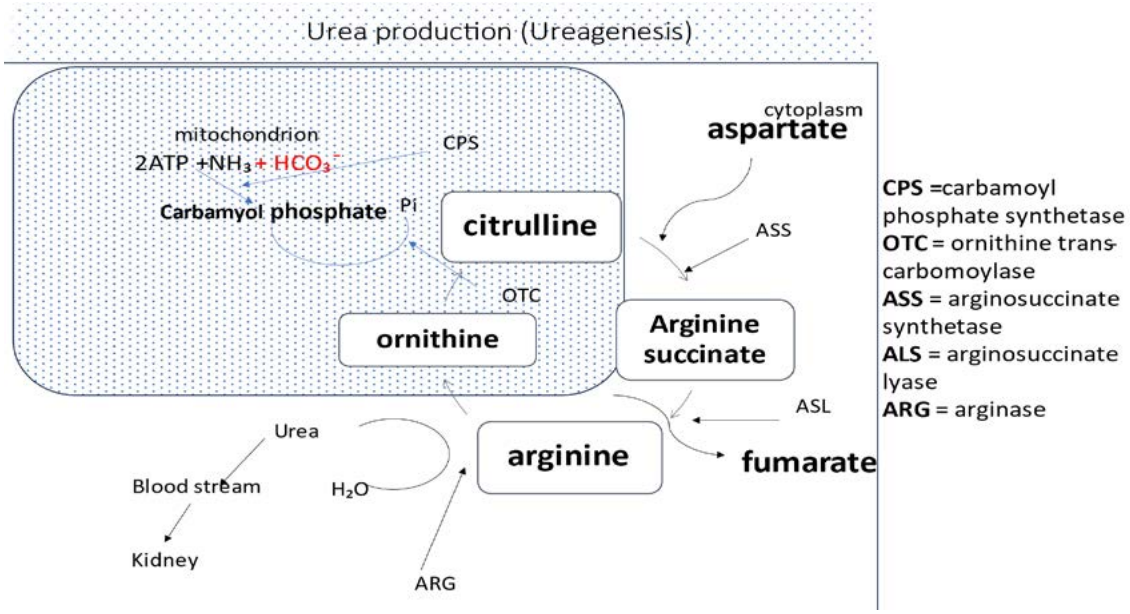

Figure 2: Hepatic urea synthetic pathway

- A 1 g/L decrease in albumin is associated with a 3.7 mEq/L increase in BE.
- A 1 g/L decrease in albumin is associated with a 0.25 mEq/L decrease in anion gap.

Hypoalbuminemia underestimates an anion gap.

Ketogenesis and ketoacids

Ketogenesis, in hepatic mitochondrial cells, is the salvage pathway for acetyl-coenzyme A, i.e. when carbohydrates and fat are incompletely oxidised. Ketoacids, 3-hydroxybutyrate, acetoacetic acid, and acetone dissociate in physiological pH to produce hydrogen ions. This may lead to ketoacidosis. Net production of ketones, as well as urinary excretion, is controlled by feedback mechanisms leading to reduced endogenous acid production if the pH decreases, and increased ketone production if the pH increases. This rapid up- and downregulation applies to both hepatic ketogenesis and lactate production. Hepatic ketogenesis is negligible and does not cause significant acidosis in normal conditions. However, starvation, massive alcohol consumption, or defective glucose transport can cause ketogenesis and substantial metabolic acidosis. Ketone bodies are utilised by extrahepatic cells, the brain, and the heart as an energy source.

Urea production

Neurotoxic weak acid $NH4^+$ arises during protein breakdown. NH_3 is processed in the liver (urea cycle). For every 1 mol of urea

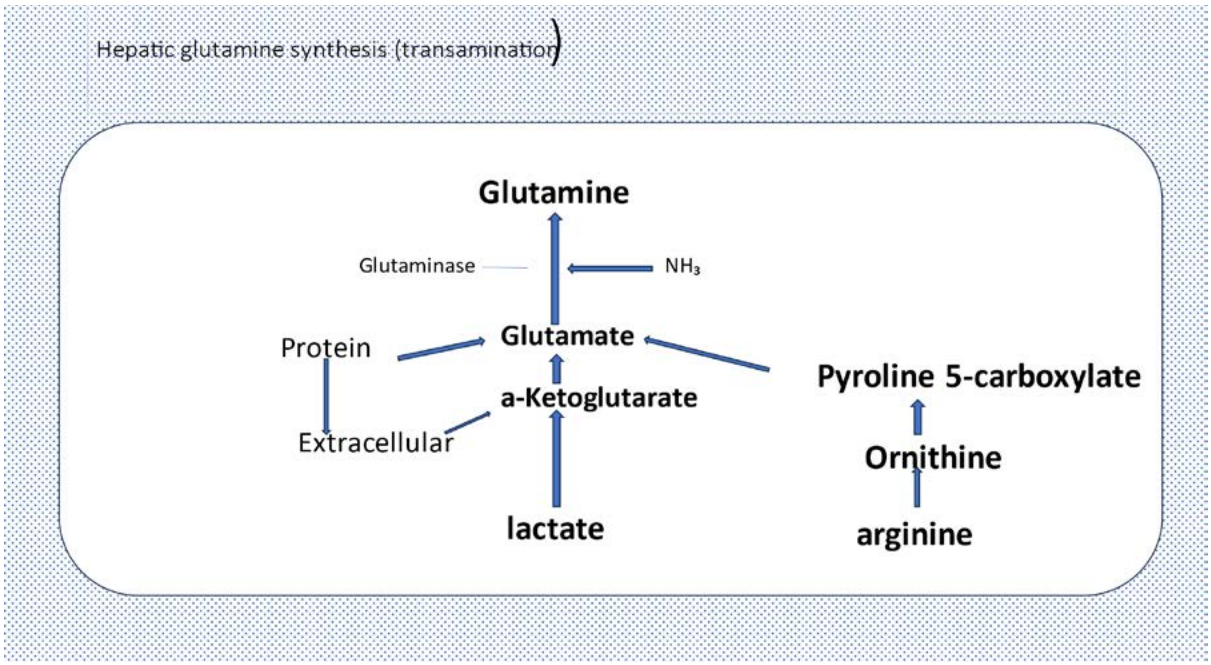

Figure 3: Hepatic transamination

generated, 1 mol of bicarbonate is consumed. This is an acidifying process (Figure 2 above). In acute metabolic acidosis, NH_3 is consumed (transamination) to generate glutamine instead of urea (Figure 3 above). Glutamine is subsequently taken up by the proximal convoluted tubules (PCTs) and catabolised to generate bicarbonate and glucose.

Transamination for glutamine synthesis (illustrated in Figure 3 below)

Alkalinising factors in patients with liver disease

In chronic liver disease, mixed respiratory and metabolic alkalosis are the main acid-base disorders.

- Ascites/hepatic hydrothorax → hypoxaemia and hyperventilation.
- Hyperammonemia and hepatic encephalopathy induce hyperventilation.
- Hepatopulmonary syndrome/portopulmonary hypertension aggravates dyspnoea.
- Secondary hypoaldosteronism induces metabolic alkalosis.
- Hypoalbuminemia is metabolic alkalosis.

Kidneys

The biochemistry of the ultrafiltrate in the PCTs is the same as in plasma. All components of the plasma are filtered through, except blood and high molecular weight substances. It is the function of the tubules to reclaim filtered substances. In Figure 4 below, sodium is reclaimed at the expense of urine acidification. The bicarbonate derived from peritubular carbonic anhydrase activity is reabsorbed with sodium through the Na-HCO_3 symporter system. There is no loss nor gain of any substance.

However, in acute metabolic acidosis, bicarbonate is preserved, and the conjugate base is filtered instead (B^-). There is a net gain of bicarbonate (generation) and a loss of a proton.

In addition, partial restoration of the acid-base balance is achieved through increased renal ammonia genesis and gluconeogenesis from plasma glutamate; and catabolism of glutamine (Figure 5 below).

Within 1–3 hours of acute acidosis, there is a 2–3 multiplied increase in hepatic glutamine synthesis (transamination). The following activities are accelerated:

- Glutamine is taken up by peritubular cells of PCTs from both circulation and luminal fluid. A specific transport system facilitates absorption from the venous site.
- Activation of apical Na/H antiport, which leads to the generation of bicarbonate. The Na/H antiport system also promotes the reabsorption of bicarbonate on the basolateral site.
- Glutamine is taken up by mitochondria and subjected to mitochondrial enzymatic activities. Glutaminase deaminates glutamine to glutamate, and glutamate is further deaminated by dehydrogenase to form α-ketoglutarate. In both processes, a molecule of ammonia is generated.
- α-Ketoglutarate enters the tricyclic acid (TCA) cycle with a subsequent generation of 2 mol bicarbonate.

Analysing the above processes:

- 1 mol HCO_3^- is generated through acidification of urine (Na/H antiport activity).
- 2 mol HCO_3^- is generated per mol of α-ketoglutarate.
- 2 mol NH_3 is generated by the mitochondrial deamination process.
- Hydrogen is excreted as ammonia salts (-$NH4^+$).
- Activation of the Na-HCO_3^- symporter system promotes the reabsorption of the product.
- In the distal convoluted tubules, HCO_3^- is preferentially reabsorbed in exchange for other anions.

In chronic acidosis, some of the acute adaptations are partially compensated and the plasma glutamine falls to about 70%. The kidney, however, continues to extract more than a third of glutamine. Renal glutamine catabolism is sustained due to increased expression of genes encoding mitochondrial

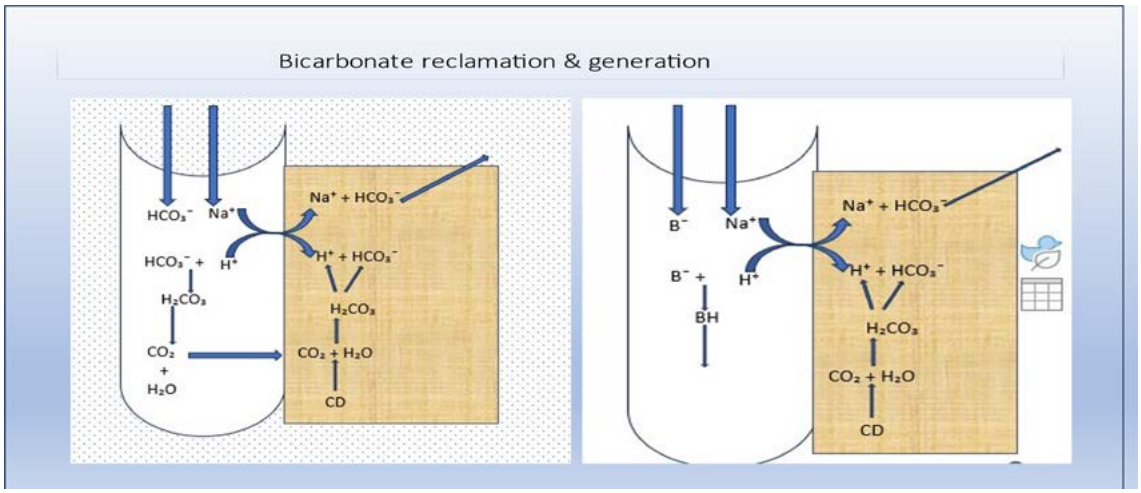

Figure 4: Bicarbonate reclamation and generation

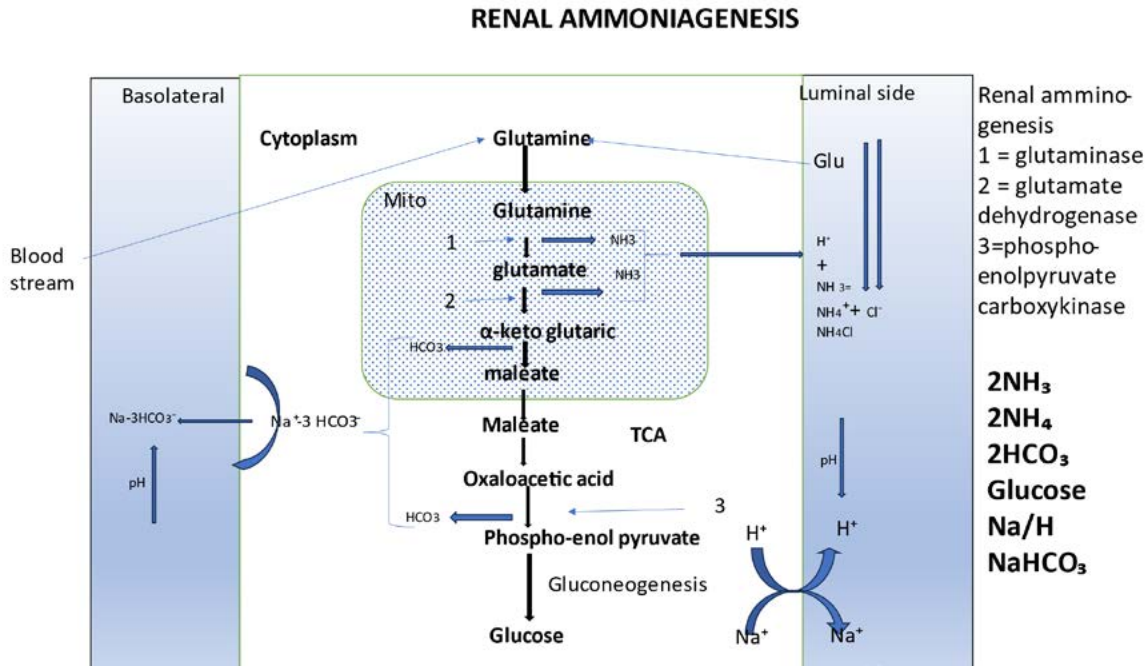

Figure 5: Ammonia genesis

glutaminase and glutamine dehydrogenase, cytoplasmic phosphoenolpyruvate carboxykinase (PEPC), apical Na/H antiport, and basolateral Na-bicarb symporter systems.

In addition, phosphate becomes important as a buffering agent.

Definition of concepts and useful terminology

Acid

A substance that donates a proton in a solution. A strong acid completely transfers its protons to water, leaving no undissociated molecules in a solution. Its conjugate base has a negligible tendency to be protonated (to abstract protons) in an aqueous solution. Weaker acids only partially dissociate in aqueous solutions and, therefore, exist in the solution as a mixture of acid molecules and their constituent ions. Strong acids have their equilibria shifted towards the right and thus have larger acidity constants (Ka); weaker acids have their equilibria shifted towards the left and smaller acidity constants. The strength of an acid depends on the number of protons it can donate.

Base

An acceptor of a proton in a solution.

A protein molecule can be both an acid and a base because proteins can accept an acid and donate a base.

Alkali

A substance that can donate a hydroxyl ion and can also accept a proton in a solution. All alkalis are bases, but not all bases are alkalis.

Standard bicarbonate

The concentration of bicarbonate in a sample of plasma should be kept under precise "standard" conditions, i.e. 37 °C and $PaCO_2$ of 40mmHg or 5.3 kPa. These changes are chosen to eliminate the respiratory contribution to acid-base status.

Actual bicarbonate

A concentration of bicarbonate measured in plasma without correction. It reflects the contribution of both respiratory and metabolic components of acid-base balance.

Base excess/deficit

The amount of strong univalent acid (HCL) or base (NaOH) required to titrate 1 L of blood back to pH 7.40. BE and deficit considers all buffers in the blood sample and is therefore considered a more accurate assessment of the metabolic component of the patient's acid-base status.

Buffers

Special protein or enzyme molecules function like a sponge to "mop up" hydrogen ions. They work effectively at very narrow margins. Humans have buffers operating in both intracellular and extracellular environments. Extracellular buffer proteins include the carbonic/bicarbonate system, phosphates, and ammonia.

Acidaemia and alkalaemia

These concepts indicate disturbances of pH in extracellular fluid. Alkalaemia: pH > 7.40. Acidaemia: pH < 7.40.

Acidosis and alkalosis

Refer to processes occurring at the cellular level that, if left uncorrected, would result in pH changes (acidaemia or alkalaemia). Acidosis/acidaemia and alkalosis/alkalaemia cannot be used interchangeably. Acidosis and alkalosis may still apply even if the pH is normal. For example, the patient may be simultaneously producing excessive but equal amounts of an acid and base, such that they balance each other out. In this case, the pH will be normal, but the underlying pathophysiological processes will still be present.

"Acidosis can exist without acidaemia, but acidaemia cannot prevail without acidosis."

Avoid sampling and analysing pitfalls.

- Obtain blood samples aerobically and aseptically.
- In the presence of an indwelling arterial catheter, remove about 5 ml of flushing solution from the cannula before actual sampling.
- Heparinise the sampling syringe to protect the microtubes of the ABG machine from clotting.
- Heparin is an acid and too much of it would influence the determination of $[H^+]$ and therefore pH levels.
- The presence of air bubbles allows CO_2 and O_2 to diffuse in or out of the bubbles and alter results within minutes, especially during transportation.
- The sample must be analysed at the patient's temperature – the results are always corrected for temperature.
  - Henry's law. The amount of gas going into a solution is inversely proportional to temperature. In hypothermia, more gases would go into a solution, especially carbon dioxide, thus giving an alkalotic picture. However, total carbon dioxide will be the same.
  - Temperature and vapour pressure. A direct relationship exists between the two. The higher the temperature, the higher the vaporisation process and the lower the partial pressure of gases.
  - pKa and temperature chemical reaction. Temperature affects the rate of chemical reactions of the buffering solutions.
- The sample should be promptly analysed. If there is a delay in sample analysis, keep the sample on ice to slow down the rate of metabolism (can be delayed up to one hour).
- Put a stopper or cap to prevent arterial blood from interacting with oxygen in the air.

Blood gas machine

- A box full of electrodes arranged in a specific order. Each electrode is designed to perform specific functions and they are governed by different physical principles and laws of physics (beyond the scope of this talk).
- The average shelf life of electrodes is 6–12 months, depending on how often they are used.
- Electrodes should be regularly inspected for protein and debris accumulation as well as the integrity of protective plastic membranes.
- Daily calibration must be done for correct results.
- The incorporated automatic temperature calibration system must be kept intact.

Arterial blood gas analysis and interpretation

Be systematic and group parameters belonging together.

Oxygenation adequacy (indices of oxygenation)

Tension-based indices

Arterial partial pressure of oxygen (PaO_2).

PaO_2 alone has no value. Relate it to inspired oxygen concentration (FiO_2). A patient registering a PaO_2 of 100 mmHg at 100% oxygen is relatively hypoxemic. PaO_2 can also be used as a function of oxygen cascade: delivery of oxygen to the lungs (respiratory mechanics), transfer of oxygen to the blood (diffusion laws), carriage of oxygen by the blood (oxygen-haemoglobin dissociation curve), delivery of oxygen to the tissues (DO_2), release of oxygen to the tissues (oxygen-haemoglobin dissociation curve and Bohr effect), and return of oxygen to the lungs (mixed venous sats).

$PA\text{-}aO_2$ (Alveolar-arterial oxygen tension difference):

- Normal $PA\text{-}aO_2$ (extra-alveolar causes): hypoventilation, low FiO_2, low barometric pressure (high altitude), ventilator-related.
- High $PA\text{-}aO_2$ (intra-alveolar causes): intrapulmonary shunt, diffusion defect, dead space ventilation, increased peripheral oxygen extraction.

PaO_2/FiO_2 ratio. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Familiarise yourself with the diagnostic criteria of both.

Oxygen index (OI)
$OI = FiO_2 \times$ mean arterial pressure (MAP) / PaO_2. Takes into consideration respiratory mechanics. Mean airway pressure: 25% good, 25–40% high mortality, and = 40% needs extracorporeal membrane oxygenator (ECMO).

Respiratory index (RI)
$RI = PA - aO_2 / PaO_2$. Normal is > 1, 1–5 is V/Q mismatch, < 5 is a physiological shunt.

Content-based indices

Venous admixture (Qs/Qt):

$$Qs = \frac{Cc'O_2}{Cc'O_2} - \frac{CaO_2}{CvO_2}$$

Co-oximetry:

- HBO_2. Haemoglobin dissociation curve, haemoglobin concentration, type of haemoglobin, and environment in which the haemoglobin operates.

- COHB. Cigarette smoking and environmental pollution/ automobile exhaust emissions. A small percentage is a product of extravascular haemolysis.
- MetHB. Oxidized haemoglobin. It is normally kept under 1%.
- Fetal haemoglobin (FFHB).

Carbon dioxide

Adequacy of respiration. The balance between the production and elimination rates.

Electrolyte analysis

This is a topic on its own and beyond the scope of this talk. However, it is worth mentioning here, based on clinical practice that metabolic alkalosis causes hypokalaemia and severe hypokalaemia sustains metabolic alkalosis. It may be extremely difficult to correct hypokalaemia despite copious administration of potassium, without addressing causes of metabolic alkalosis.

Metabolic alkalosis causes hypokalaemia:

- At cellular level: Electrolyte shift. Intracellular hydrogen is exchanged for extracellular potassium.
- Renal level: Na/K antiport promoted at expense of Na/H antiport system.
- Secondary hypoaldosteronism, due to contracted extracellular volume, promotes Na reabsorption at the expense of potassium.

Chronic hypokalaemia sustains metabolic alkalosis:

- Cellular level: Electrolyte shift. Intracellular potassium will be shifted in exchange for hydrogen. However, hydrogen is generated with bicarbonate.
- Chronic hypokalaemia stimulates PCTs to generate ammonia via glutamine activity. This generates bicarbonate.

Therapeutic classification of metabolic alkalosis:

- Saline responsive: U $[Cl^-]$ < 10 mmol/L

  Vomiting, contracted extracellular fluid, preservation of chloride by the kidney. This alkalosis responds well to saline administration, unless on diuretics.
- Saline resistant: U $[Cl^-]$ > 20 mmol/L

Familiarise yourself with the broad causes of metabolic alkalosis and acidosis and their physiological effects.

Indices of perfusion

BE, lactate, and mixed venous sats.

Analysis of metabolites

Lactate, glucose, and bilirubin (a topic on its own).

Acid-base status (HCO_3^- based vs. biochemical approach)

Henderson-Hasselbalch equation

This equation describes the relationship between pH, pK_a, and [acid] and [base] concentration:

$$pH = pK_a + \log \frac{[HCO_3^-]}{[H_2HCO_3]}$$

$$pH = pK_a + \log \frac{[HCO_3^-]}{[0.03 \times PCO_2]}$$

$$pH = 6.1 + \log \frac{[20]}{[0.03 \times 40]}$$

$$pH = 6.1 + 1.3 = 7.40$$

Take note:

- Ka is the dissociation constant of H_2HCO_3; pK_a is the negative common logarithm of Ka.
- The pH is the negative common logarithm of hydrogen ion concentration. Briefly, pH is proportional to bicarbonate and inversely proportional to PCO_2. However, bicarbonate is a dependent variable and its relationship with pH is non-linear.
- The emphasis is on the ratio of HCO_3^- / 0.03 × PCO_2 and not the individual components.
- If the ratio remains 20, the pH will be normal.
- The ratio forms the basis of compensation. An increase in one component should be associated with an increase in a second component by the same margin to keep the pH constant.
- Compensation dictates that changes should be in the same direction. A convergent or divergent picture suggests mixed acid-base status. Metabolic acidosis will be compensated by respiratory alkalosis. The opposite is also true.
- Compensation is never complete.

Stewart's approach to acid-base

An alternative approach to deciphering the complex acid-base status of patients. It takes into consideration the pathophysiology of diseases and organ interactions.

Principles:

- State of electroneutrality. Negatively charged ions are exactly equal to positively charged particles. An increase in one negatively charged particle, for example, will be accompanied by a decrease in another negative particle by the same margin or charge.
- Law of mass conservation: An amount of a substance in the body remains constant unless generated or removed.
  - Routinely measured cations: Na/K/Ca/Mg.
  - Unmeasured cations: proteins, lithium, and aluminium.
  - Commonly measured anions: chloride and bicarbonate.
  - Other anions: $SO4^{2-}$, H_2PO4^{2-}, and albumin.
  - Organic anions: citrate, lactate, alcohol, and other toxins.

Fundamental differences between Stewart's approach and bicarbonate-centred models

- Hydrogen and bicarbonate are not independent determinants of acid-base status, but the result of changes in other systems. Hydrogen and bicarbonate ion concentrations are dependent on combined strong ion difference (SID), total weak acid concentration, and partial pressure of CO_2.
- BE is the overall measure of metabolic acid-base status. The amount of strong univalent acid (HCL) or base (NaOH) required to titrate 1 L of blood back to pH 7.40. Normal range: -3–3.
- Weak acids (albumin and phosphate) are also important in the determination of acid-base status. Phosphate participates more in chronicity. Weak acids play a role opposite to SID. Hyperalbuminemia (↑ weak acid concentration) causes acidosis, while low albumin (↓ total weak acids) induces alkalosis.
- The principal metabolic factor is the SID. Three independent controllers of acid-base status: CO_2, SID, and total concentration of weak acids.
  - Strong ions dissociation completely in a solution, NA^+, K^+, Cl^-.
  - Weak ions dissociation incompletely in a solution, HCO_3^-,
  - $PO4^-$ and albumin.
  - Lactate is regarded as a strong ion as it dissociates almost completely in a solution.
  - Measured SID: Sum of all plasma cations minus anions that are measured routinely in practice.
  - Na^+ is a strong cation while Cl^- is a strong anion in plasma, therefore SID = Na - Cl (40 - 42 mmol/L).
  - ↑ SID suggest alkalosis, ↑ Na^+ or ↓ Cl^-, and therefore ↑ HCO_3^-.
  - ↓ SID suggest acidosis, ↓ Na^+ or ↑ Cl^-, and therefore ↓HCO_3^-.
  - In metabolic acidosis strong ions squeeze HCO_3 out, the opposite is true for alkalosis. For every 1 mEq/L in NACL difference, BE will change by 1 mEq/L in a negative direction for ↓ SID and positive for ↑ SID, i.e. in the same direction.

Calculated SID = $[Na^+ + K^+]$ - [albumin × 0.2 + phosphate × 1.5 + $Cl^- + HCO_3^-$]

Therefore, an overall BE:

- Lactate base effect = 2 - measured lactate.
- Albumin base effect = 0.25 (normal - measured albumin level).
- SID base effect = $(Na^+ - Cl^- - 40)$.

Consider other changes in strong ions and weak acids, especially in organ dysfunction of the kidneys and liver. If the above three factors do not explain observed changes in the BE, then one or more other factors are involved.

Putting it all together

BE = [Na - Cl - 40] + [2 - measured lactate] + [0.25 (normal - measured albumin)] + OI

OI = BE - [Na - Cl - 40] + [1 - measured lactate] + [0.25 (normal - measured albumin)]

Practical exercise

An intubated and ventilated patient is transferred from the accident and emergency department for urgent laparotomy. Large bowel obstruction is the working diagnosis. The patient has had saline resuscitation.

Analysis of blood gas results:

Biochemistry: Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28 g/L, lactate 7.0 mmol/L

ABG: pH 7.20, PCO_2 40 mmHg, bicarbonate 15 mmol/L, BE -14.5 mmol/L

Bicarbonate based approach.

- Acidaemia, significant base deficit. This suggests metabolic acidosis.
- Anion gap: $(Na + K) - (HCO_3 + Cl^-) = (145 + 3) - (117 + 15) = 16$. It appears as normal anion gap metabolic acidosis.
- However, bicarbonate and PCO_2 converge. This suggests mixed respiratory and metabolic acidosis. It cannot be a compensated picture.
- Which one is primary and secondary? Test it using Winter's formula.
  - Expected PCO_2 = 1.5 (bicarbonate) + 8 = 1.5(15) + 8 = 30.5 mmHg. The measured PCO_2 is 40 mmHg. Therefore, it would appear that PCO_2 is elevated.
  - Expected bicarbonate = 0.44 (PCO_2) + 7.6 = 24.5. The calculated bicarbonate is 15 mmol/L. A mixed picture would therefore make sense.

But chloride is high (117 mmol/L).

Stewart's approach (physical chemical approach)

Biochemistry: Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28g/L, lactate 7.0 mmol/L

ABG: pH 7.20, PCO_2 40 mmHg, bicarbonate 15 mmol/L, BE -14.5 mmol/L

- BE = SID effect + lactate effect + weak acids effect + OI
- (Na – Cl - 40) + (2 - 7.0) + 0.25(40 - 28) + OI
- -12 + -2 = -14.0
- OI = -14.5 + 14 = -0.5 (insignificant contributor)
- Therefore:
  - Change in BE is secondary to pure hyperchloremia.
  - Partly offset by low albumen level.
  - Partly aggravated by lactate.
  - Insignificant contribution of OI to acid-base derangement.

See Table I - commonly used fluids in theatre.

Table I: Comparison of biochemistry of commonly used fluids and extracellular fluid compartment

Common fluids

	ECF Compartment	Balsol	Ringers	Mod Ringers
Na^+	142	130	131	131
K^+	5	4	5.4	5.4
Mg^{++}	1	1.5		
Ca^{++}	2.5		1.8	
Cl^-	105	110	112	108
HCO_3^-	27	27		
Lactate			29	29
Osmolality	310	273	278	273

Treatment options of hyperchloremic metabolic acidosis using fluids in table I

PlasmaLyte (Balsol)

Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28 g/L, lactate 7.0 mmol/L, SID = 28, BE = -14.5

PlasmaLyte:

- Na = 130 mmol/L and chloride 110 mmol/L
- Combined SID: (145 + 130) / 2 - (117 + 110) / 2
- 137.5 - 113.5 = 24
- 24 - 28 = -4
- Therefore, final BE: -4 + -14.5 = -18.5 (For every 1 mEq/L in NACL difference, BE will change by 1 mEq/L in the same direction.)

Ringer's lactate

Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28 g/L, lactate 7.0 mmol/L, SID = 28, BE = -14.5

Ringer's lactate:

- Na 131 mmol/L and chloride 112 mmol/L
- Combined SID: (145 + 131) /2 - (117 + 112) / 2
- 138 - 114.5 = 23.5
- 23.5 - 28 = -4.5
- Final BE: -4.5 + -14.5 = -19.0

Half normal saline

Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28 g/l, lactate 7.0 mmol/L, SID = 28, BE = -14.5

Half normal saline:

- Na 77 mmol/L and chloride 77 mmol/L
- Combined SID: (145 + 77) / 2 - (117 + 77) / 2
- 111 - 97 = 14
- Final BE: 14 - 28 = 14 = -14.5 + -14 = -28.5

Sodium bicarbonate (50 mEq/L)

Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28 g/l, lactate 7.0 mmol/L, SID = 28, BE = -14.5

50 mEq/L sodium bicarbonate:

- Combined SID: (145 + 50) / 2 - (117 + 0) / 2 = 97.5 - 58.5 = 39 - 28 = 11
- Final BE: -14.5 + 11 = -3.5 (better)

Sodium bicarbonate (10 mEq/L)

Na 145 mmol/L, K 3.0 mmol/L, Ch 117 mmol/L, albumin 28 g/l, lactate 7.0 mmol/L, SID = 28, BE = -14.5

10 mEq/L sodium bicarbonate:

- Combined SID: (145 + 10) / 2 - (117 + 0) / 2 = 77.5 - 58.5 = 19
- 19 - 28 = -9
- Final BE: -14.5 + -9 = -23.5
- Hypo-osmolar bicarbonate

Pharmacological intervention?

- Forced diuresis in volume replete patient.
- Loop diuretics.

Reconstitute your own fluid.

You may also reconstitute your fluid, e.g. adding sodium to 5% dextrose water solution.

Bibliography

- Anthony-Cahill SJ, Mathews CK, Van Holde K E, Appling DR. Biochemistry. 4th ed. Pearson Canada Inc, 2013. p. 38-44.
- Barrett KE, Barman SM, Boitano S, Brooks H. Ganong's review of medical physiology. 23rd ed. McGraw-Hill Medical; 2009. p. 679-85.
- Joubert I. Blood gas interpretation workshop. University of Cape Town; 2017.
- McMurry JE. Fundamentals of organic chemistry. 7th ed. Cengage Learning; 2010. p. 18-26.
- Nolte D. Principles of measurement arterial blood gas and electrodes: part 1 refresher 2018. University of Cape Town; 2018.Omar S. Electrochemistry (how a blood gas machine works): part 1 refresher 2018. University of the Witwatersrand; 2018.
- Sheiner B, Lindner G, Reiberger T, et al. Acid-base disorder in liver disease. J Hepatol. 2017;67:1062-1073. https://doi.org/10.1016/j.jhep.2017.06.023.
- Story DA. Stewart acid-base: a simplified bedside approach. Anesth Analg. 2016;123(2):511-5. https://doi.org/10.1213/ANE.0000000000001261.

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FCA REFRESHER COURSE

The physics of neuromuscular monitors in anaesthesia

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Introduction

Neuromuscular monitoring plays a crucial role in ensuring patient safety during anaesthesia. It allows anaesthesiologists to accurately assess the level of muscular blockade, enabling them to administer medications and adjust dosages accordingly. Underlying neuromuscular monitoring is a complex interplay of physics principles, which govern the functioning and interpretation of these devices. In this paper, we will explore the physics behind neuromuscular monitors, including single-twitch, double-burst, and post-tetanic count, and their significance in enhancing patient care.

The physiology of neuromuscular blockade

Before delving into the physics behind neuromuscular monitors, it is essential to understand the physiological basis of neuromuscular blockade. Skeletal muscles are controlled by signals transmitted from motor neurons through the neuromuscular junction (NMJ). Here, acetylcholine released by the nerves facilitates the transmission of electrical impulses, ultimately producing muscle contraction.[1]

Neuromuscular monitors consist of surface electrodes, stimulating electrodes, and sensors that measure the resulting muscle response. The primary objective is to assess the transmission of nerve impulses across the NMJ by stimulating the nerve or muscle and quantifying the response parameters.

Neural stimulation

The neural response depends on current density, not voltage. To achieve a consistent and repeatable maximal response, the current density must be greater than what is needed to get a maximal response.[2]

Using Ohm's law[3] where: V = IR

Potential difference (voltage) = current × resistance

Current = voltage / resistance

To produce a constant current with changes in skin resistance (normal between 500 and 2 000 Ω) requires a change in voltage. Current nerve stimulators are constant current stimulators, which through feedback, detect changes in the current delivered and alter the voltage accordingly, so the desired current is always given.

The controls on the nerve stimulator determine the required current, mode of stimulation and frequency. A microprocessor determines voltage output from the battery, receiving feedback from the current generator and altering voltage requirements. The oscillator provides the pulse in the current generator and the current generator delivers current to the patient.[2]

Determinants of neural stimulation

Table I: Factors determining nerve response to a stimulus[4]

Rheobase of the nerve	The minimum current required to depolarise a nerve is given an infinite duration of stimulation.
Chronaxie of the nerve	The minimum time required for excitation of a structure (such as a neuron) by a constant electric current of twice the threshold voltage.
Polarity of the electrodes	Negative (black electrodes) are more efficient at causing a nerve to depolarise.
Distance of the nerve from the electrode	The further the nerve is from the electrode, the more current is needed to stimulate it. Coulomb's law:[3] current required = minimal current / distance[2]
Area of the electrode	Smaller electrodes will produce a greater current density.

Patterns of stimulation

Single-twitch

A single-twitch stimulation involves the application of a single electrical impulse to the nerve or muscle.[5] A single pulse, 0.2 ms in duration, produces a short-duration muscle contraction, providing essential information about baseline neuromuscular function and the degree of muscular blockade.[6] The physics behind single-twitch monitoring involves understanding the electrical properties of the tissue, nerve conduction, and the mechanics of muscle contraction.

i. Electrical properties of tissue

Tissues have varying electrical properties that influence the transmission of electrical signals. These properties include

conductivity, resistivity, capacitance, and impedance. Conductivity refers to the ability of a tissue to conduct electrical current. Different tissues, such as muscle, nerve, and skin, exhibit distinct conductivity properties due to variations in their composition and structure. Understanding these electrical properties is crucial for accurate interpretation of the electrical signals measured during single-twitch monitoring.[4]

ii. Nerve conduction

Nerve conduction is an essential component of single-twitch monitoring. It involves the transmission of electrical impulses along the nerve fibres that innervate muscles. When a nerve is stimulated, an action potential travels along its length, leading to the release of acetylcholine at the NMJ. This chemical communication triggers the muscle fibres to contract. Understanding the physics of nerve conduction, including concepts such as action potentials, membrane potential, and ion channels, is fundamental to accurately assessing the neuromuscular response during single-twitch monitoring.[7]

iii. Mechanics of muscle contraction

The mechanics of muscle contraction are vital to interpreting the response observed during single-twitch monitoring. When a nerve impulse triggers muscle contraction, it leads to the sliding of actin and myosin filaments within the muscle fibres, resulting in tension generation. This mechanical process involves concepts such as sarcomere length, force production, and muscle-tendon mechanics. Understanding these principles aids in evaluating the strength and characteristics of the single-twitch response, providing insights into neuromuscular function.[6]

Double-burst stimulation (DBS)

DBS is used to assess the depth of neuromuscular blockade and the recovery of neuromuscular function. It involves delivering two short bursts of electrical pulses with a brief interval between them.[5] The first burst stimulates a submaximal twitch response, and the second burst assesses the fade response or the decrease in muscle contraction strength. A burst of two or three impulses is separated by 0.75 seconds. Two patterns are used, 3:2 or 3:3, representing the number of twitches in each burst. Each burst occurs at a rate of 50 Hz, (three twitches take 0.06 seconds and 2 twitches 0.04 seconds, as seen in Figure 1).[8] The physics behind double-burst stimulation includes considerations of electrical pulse synchronisation, muscle fatigue, and the mechanics of force generation.

i. Electrical pulse synchronisation

Double burst stimulation utilises two short bursts of electrical pulses to evaluate the response of the NMJ and muscle. The timing and synchronisation of these pulses are critical for accurate assessment. The physics behind this aspect involves ensuring precise timing between the two bursts, analysing the impact of pulse duration and interval, and understanding the principles of electrical circuitry. Proper synchronisation ensures consistent and reliable measurement of the muscle response and helps evaluate the level of neuromuscular blockade.

ii. Muscle fatigue

Muscle fatigue can impact the response observed during DBS. With repetitive stimulation, the muscle fibres may experience fatigue, leading to a decrease in force production. This phenomenon can result from various factors, including a limited supply of adenosine triphosphate (ATP), accumulation of metabolic by-products, and impaired muscle contractile properties. Understanding the physics of muscle fatigue allows anaesthesiologists to interpret the fade response during DBS accurately. It helps identify the depth of the neuromuscular blockade and assess the potential recovery of muscle function.

iii. Mechanics of force generation

The mechanics of force generation are integral to the assessment of muscle response during DBS. The force produced by a muscle depends on factors such as the number of active motor units, muscle fibre recruitment, and the length-tension relationship. When evaluating a fade response during the second burst, it is essential to consider the mechanics of force generation. The physics involved include understanding the principles of muscle contraction, muscle-tendon mechanics, and lever systems. This knowledge aids in quantifying the strength of muscle contractions and determining the level of neuromuscular blockade.

By considering electrical pulse synchronisation, muscle fatigue, and the mechanics of force generation, anaesthesiologists can effectively utilise DBS to assess neuromuscular function. This technique provides valuable information about the depth of neuromuscular blockade and the likelihood of recovery. Accurate interpretation of the muscle response during DBS plays a crucial role in adjusting anaesthesia administration, optimising muscle relaxation, and enhancing patient safety during surgery.

Post-tetanic count (PTC)

PTC is a technique used to evaluate the depth of neuromuscular blockade and its recovery by delivering a series of rapid, high-frequency stimuli. This results in a sustained contraction known as a tetanic contraction. The subsequent muscle twitch response following the tetanic contraction is analysed to determine the degree of neuromuscular blockade.[6] It uses the mobilised acetylcholine from a tetanic stimulation to evaluate intense blockade when no twitch is present on a Train-of-Four (TOF), three seconds after a tetanic stimulus a single twitch at one-second intervals is delivered, as seen in Figure 1.[8] The number of twitches present allows an estimation of how long it will take until T1 appears on a TOF.[5] The physics involved in PTC monitoring includes understanding the nerve refractory period, neuronal synchronisation, and the mechanics of muscle contraction.

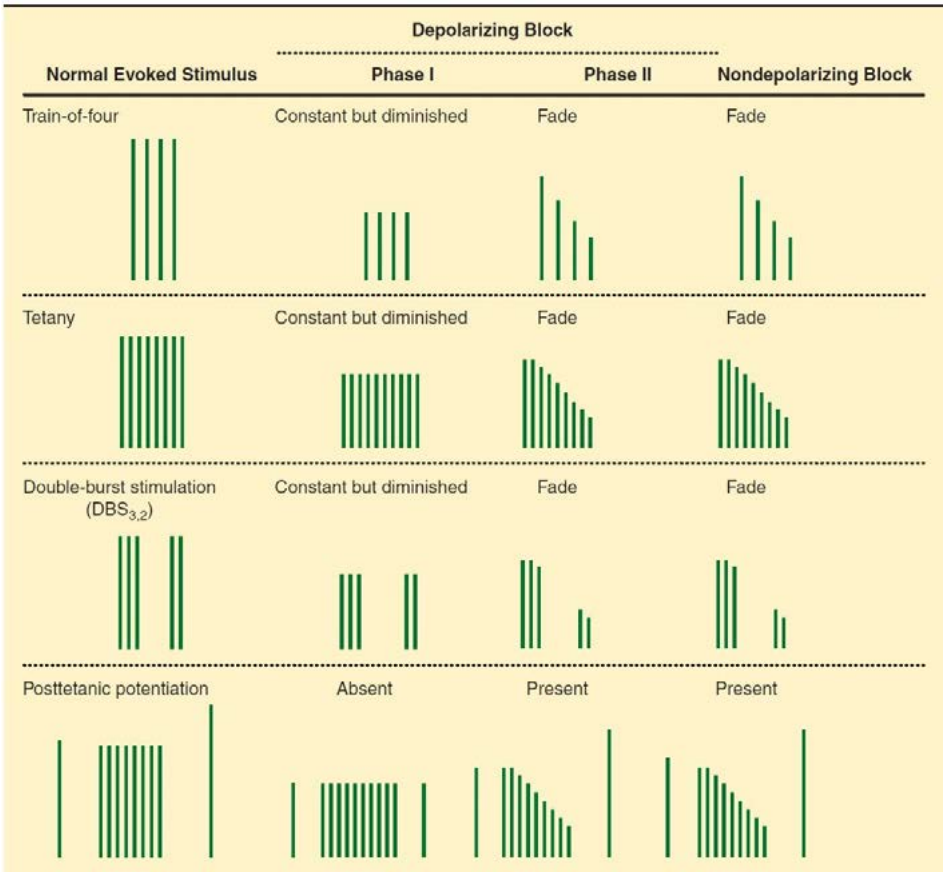

Figure 1: Evoked responses during depolarising (Phase I and Phase II) and nondepolarising block[8]

i. Nerve refractory period

The nerve refractory period is a critical factor in understanding PTC monitoring. After a nerve is stimulated, it enters a refractory period during which it is unresponsive to further stimulation. This period allows the nerve to reset and regain its excitability. Understanding the duration and characteristics of the nerve refractory period is crucial for effective PTC monitoring. The physics involved here includes studying the electrical properties of nerves and their response to stimulation.

ii. Neuronal synchronisation

Neuronal synchronisation plays a significant role in PTC monitoring. During high-frequency stimulation, multiple motor neurons may be activated simultaneously. The synchronisation of these neurons' firing patterns contributes to the generation of the sustained tetanic contraction. Monitoring the subsequent muscle twitch response following the tetanic contraction helps assess the level of neuromuscular blockade and the recovery of neuromuscular function. The physics involved in neuronal synchronisation includes understanding the electrical signals transmitted by neurons and the principles of signal superposition.

iii. Mechanics of muscle contraction

The mechanics of muscle contraction is another important aspect of PTC monitoring. During the sustained tetanic contraction, numerous muscle fibres are actively contracting simultaneously. The mechanics of force generation in muscle fibres involve principles of muscle physiology, muscle-tendon mechanics, and lever systems. Understanding these principles helps interpret the subsequent muscle twitch response following the tetanic contraction and evaluate the level of neuromuscular blockade.[9]

TOF

The TOF is another commonly used technique in neuromuscular monitoring. It involves the application of a series of four consecutive electrical stimuli to assess the level of neuromuscular blockade and the recovery of neuromuscular function, as seen in Figure 1.[8] It is a series of four twitches in two seconds (2 Hz frequency), each 0.2 ms long.[5,6]

i. Electrical stimulation

During TOF monitoring, four electrical stimuli are delivered in quick succession. The timing and characteristics of these stimuli are crucial for accurate assessment. The physics involved in the electrical stimulation include considerations of pulse duration, amplitude, frequency, and synchronisation. These parameters are carefully selected to elicit muscle responses that can be quantitatively evaluated.

ii. Muscle response

The muscle response elicited by electrical stimulation during TOF monitoring is influenced by various factors. Understanding

the physics behind muscle response is essential for accurate interpretation of the resulting data. Several principles come into play, including the recruitment of motor units, muscle fibre characteristics, and the length-tension relationship. The magnitude and characteristics of the muscle response, such as twitch height and duration, provide valuable information about neuromuscular function and the degree of blockade.

iii. Fade response

The fade response observed during TOF monitoring is a unique characteristic that helps assess the level of neuromuscular blockade. It refers to the progressive reduction in muscle contraction strength observed in response to the four consecutive stimuli. Fade can manifest as a decrease in twitch height or duration, or both.[5] The physics behind this phenomenon involves understanding the synchronisation of nerve impulses, recruitment of motor units, and muscle fatigue. Fade response is influenced by the depth of blockade and the recovery of neuromuscular function.[10]

The TOF count (TOFC) is defined as the number of detectable evoked responses, and it correlates with the degree of neuromuscular block, as follows:[8,10]

- TOFC 1: > 95% of nicotinic acetylcholine receptors (nAChRs) blocked.
- TOFC 2: 85–90% of nAChRs blocked.
- TOFC 3: 80–85% of nAChRs blocked.
- TOFC 4: 70–75% of nAChRs blocked.

Clinical use of nerve stimulating patterns[7]

- DBS: Demonstrates recovery from blockade where no objective monitor is available.
- PTC: Demonstrates recovery from intense blockade to a single twitch on TOF, i.e. the depth of block.
- TOF: Demonstrates recovery of blockade back to normal and even complete reversal.

Clinical endpoints of neuromuscular blocking agents[7]

- Deep block with no movement possible: PTC 0 or 1.
- Surgical block where movement may occur: TOF T1–T2.
- Reversal with neostigmine possible: TOF > T2.
- Return of airway reflexes: TOF ratio > 90%.

Qualitative versus quantitative monitoring

Qualitative monitoring refers to visual or tactile (i.e. holding the patient's thumb and feeling movement) evaluation of the TOFC or degree of TOF fade in response to neurostimulation provided by a peripheral nerve stimulator. Qualitative monitoring is sometimes referred to as subjective monitoring.

Quantitative, or objective, monitors measure the response of the muscle to the neurostimulation and should be used whenever they are available.[9]

Quantitative monitors

Electromyography (EMG)

EMG, a technique used by neuromuscular monitors, measures electrical activity produced by muscles. The sensors in neuromuscular monitors detect these signals, which can be influenced by electrode-skin impedance and electrode placement. Understanding the electrical properties of tissue, electronic circuitry, and the physics of signal amplification is crucial in accurately interpreting the EMG signals. The physics behind EMG involves concepts such as signals, noise, amplification, filtering, and signal processing.[7,9]

Acceleromyography (AMG)

A piezoelectric crystal is usually attached to the thumb and its acceleration is measured after having the ulnar nerve stimulated. Newton's second law is applied:[3] force = mass × acceleration. The thumb provides a constant mass, therefore the force of contraction equals acceleration. For AMG, the arm position must stay the same throughout the monitoring period, and the thumb must be free to move, unimpeded by surgical drapes or positioning. Consequently, AMG cannot be applied to an arm that is tucked at the patient's side, unless the arm is placed in a special protective device.[7,9]

Properties of an ideal nerve stimulator[4]

The following are some important properties of an ideal nerve stimulator in anaesthesia practice.

Accuracy and precision

An ideal nerve stimulator should deliver precise and accurate stimulation to assess neuromuscular function reliably. It should provide consistent and reproducible results, allowing accurate evaluation of muscle response. This accuracy is crucial for determining the appropriate dosage of neuromuscular blocking agents and ensuring patient safety.

Customisability

Different patients may have unique neuromuscular characteristics, requiring customised stimulation parameters. An ideal nerve stimulator should allow for easy customisation of stimulation parameters, such as pulse duration, frequency, and current intensity. This ensures that the stimulator can adapt to individual patient needs and provide optimal neuromuscular monitoring.

User-friendly interface

The nerve stimulator should have a user-friendly interface that is intuitive and easy to operate. Anaesthesiologists and healthcare professionals need to navigate through stimulation settings efficiently and interpret the results accurately. A clear and user-friendly interface aids in quick and efficient usage, reducing the likelihood of errors or confusion.

Multiple stimulation modes

An ideal nerve stimulator should offer various stimulation modes to cater to different clinical scenarios and preferences. Common modes include single-twitch, TOF, DBS, and tetanic stimulation. Having multiple stimulation modes allows for a comprehensive assessment of neuromuscular function and enhances clinical versatility.

Safety features

Safety is of utmost importance in anaesthesia practice. An ideal nerve stimulator should incorporate safety features to minimise the risk of adverse events. This may include visual and audible alarms to warn against excessive stimulation or prolonged muscle blockade. The stimulator should also have built-in protection against electrical shocks and short circuits, ensuring the safety of both patients and healthcare professionals.

Wireless connectivity and integration

Incorporating wireless connectivity in a nerve stimulator provides convenience and flexibility in clinical practice. It allows for seamless communication with other monitoring devices and anaesthesia equipment. Integration with data management systems enables real-time monitoring, data logging, and analysis, facilitating comprehensive patient assessment and documentation.

Portability

Portability is crucial in anaesthesia practice, particularly in operating rooms and other clinical settings. An ideal nerve stimulator should be compact, lightweight, and battery-powered for easy mobility. This allows for convenient transportation and use in various clinical environments, improving workflow efficiency and patient care.

Durability and longevity

A nerve stimulator should be designed to withstand the demands of daily clinical use. It should be robust, durable, and able to survive frequent handling and accidental drops. Long battery life is desirable to prevent disruptions during critical procedures.

Cost-effectiveness

While maintaining high quality and performance, an ideal nerve stimulator should be cost-effective. It should provide value for money, considering its accuracy, reliability, and durability. Cost-effectiveness ensures wider accessibility and utilisation, benefiting healthcare facilities of all sizes.

Compatibility

An ideal nerve stimulator should be compatible with various monitoring systems and accessories commonly used in anaesthesia practice. This includes integration with anaesthesia workstations, patient monitors, and other devices. Compatibility enables seamless data exchange and aids in comprehensive patient monitoring.

Conclusion

Neuromuscular monitors in anaesthesia rely on the application of various physics principles to accurately assess the level of neuromuscular blockade. From the single twitch response to the DBS and PTC, each technique provides valuable information about neuromuscular function and the depth of blockade. By leveraging physics principles such as EMG, biomechanics, and electrode impedance, anaesthesiologists can effectively monitor neuromuscular blockade, tailor anaesthesia administration, and ensure patient safety.

The comprehensive understanding of the physics underlying neuromuscular monitors enhances patient care by reducing the risk of complications associated with inadequate paralysis or excessive muscle relaxation during surgery. Incorporating physics into the interpretation and use of neuromuscular monitors allows anaesthesiologists to make informed decisions based on quantitative data, improving the efficacy and safety of anaesthesia administration. Advances in neuromuscular monitoring technology will further deepen our understanding of the physics behind these devices and contribute to continuous improvement in patient care in the field of anaesthesia.

References

1. Chambers D, Huang C, Matthews G. Synapses and the neuromuscular junction. In: Huang C, Chambers D, Matthews G, editors. Basic physiology for anaesthetists. 2nd ed. Cambridge: Cambridge University Press; 2019. p. 231-8. https://doi.org/10.1017/9781108565011.056.
2. Kopman AF, Lawson D. Milliamperage requirements for supramaximal stimulation of the ulnar nerve with surface electrodes. Anesthesiology. 1984;61(1):83-5. https://doi.org/10.1097/00000542-198407000-00015.
3. Davis PD, Kenny GN. Basic physics and measurement in anaesthesia. Edinburgh: Butterworth-Heinemann; 2015.
4. McGrath CD, Hunter JM. Monitoring of neuromuscular block. Contin Educ Anaesth Crit Care Pain. 2006;6(1):7-12. https://doi.org/10.1093/bjaceaccp/mki067.
5. Cross ME, Plunkett EVE. Neuromuscular blockade monitoring. In: Plunkett EVE, Cross ME, editors. 2nd ed. Physics, pharmacology and physiology for anaesthetists: key concepts for the FRCA. Cambridge: Cambridge University Press; 2014. p. 119-23. https://doi.org/10.1017/CBO9781107326200.049.
6. Miller RD. Miller's anesthesia. 8th ed. Philadelphia: Churchill Livingstone; 2015.
7. Duţu M, Ivaşcu R, Tudorache O, et al. Neuromuscular monitoring: an update. Rom J Anaesth Intensive Care. 2018;25(1):55-60.
8. Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's clinical anesthesiology. 5th ed. New York: McGraw-Hill; 2013.
9. Appadu B, Vaidya A. Monitoring techniques: neuromuscular blockade and depth of anaesthesia. Anaesth Intensive Care Med. 2008;9(6):247-50. https://doi.org/10.1016/j.mpaic.2008.04.001.
10. Lee CM. Train-of-4 quantitation of competitive neuromuscular block. Anesth Analg. 1975;54(5):649-53. https://doi.org/10.1213/00000539-197509000-00021.

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Intermediary metabolism

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In humans, chemical unity in diversity prevails as metabolic pathways are coordinated, regulated, and integrated to protect the body against metabolic catastrophes. The end product of one metabolic pathway is connected to another metabolic pathway of the same or another metabolite. A basic understanding of the normal metabolic pathways and their abnormality is the foundation in the management of patients subjected to the stress of anaesthesia and surgery. Objective clinical evaluation, investigations, and perioperative risk stratification of patients are based on understanding the fundamentals of intermediate metabolism.

Keywords: intermediary metabolism, essential intracellular chemical processes

Introduction

Metabolism refers to the hormonal coordinated, multistep enzyme-mediated chemical reactions and energy transformation occurring in a living organism.[1] Intermediary metabolism refers to the sum of essential intracellular chemical processes and pathways by which nutritive material (carbohydrates, proteins, and fats), post-digestion and absorption, is converted into cellular components.[1,2] The basic high potential substrates, such as glucose from carbohydrates, amino acids (AA) from proteins, free fatty acids (FFA) and glycerol from fats, undergo oxidation (process of oxygen + substance combination with electron/hydrogen removal) to substrate at lower potential. In the mitochondria, under aerobic conditions, the tricarboxylic acid (TCA) cycle /citric acid cycle occurs, consuming glucose and fat breakdown products such as acetyl-CoA and AA.

Reduced coenzymes, such as nicotinamide adenine dinucleotide (NAD^+), nicotinamide adenine dinucleotide phosphate ($NADP^+$), and flavin adenine dinucleotide (FAD), pick up the removed hydrogen from oxidation in the process called electron transport chain.[1] The final product of the metabolic process yields CO_2, H_2O, and energy essential for survival. Less energy can also be generated anaerobically via glycolysis with the production of lactate. The high energy phosphate (PO_4^{3-}) bonds in adenosine triphosphate (ATP) make it the energy currency of the cell.[1]

Energy requirements

Energy balance describes the difference between caloric intake and energy output. During positive energy balance (caloric intake > energy expenditure from thermogenesis and work), the body stores energy increasing the risk of weight gain. In a fasted state and starvation, caloric intake do not meet energy requirements (i.e. negative energy balance); endogenous stores such as glycogen, body protein, and fat are catabolised.[3] Energy production is constantly required for multiple cellular functions in a living organism.

Energy units are calories or kilocalories (kcal); 1 kcal = 1 000 calories. Kilojoules (kJ) are other units of energy (1 kcal = 4.18 kJ). The basal energy expenditure (BEE), also called basal metabolic rate (BMR), is about 200 kcal/day for an average-sized man. The BEE falls by about 10% during sleep and goes up by 40% during exercise.[1]

Intermediary metabolism has pathways that are anabolic and catabolic in nature.[1,3] The starve-feed cycle, energy availability, and regulatory mechanism for the metabolism determine the direction of the intermediary metabolic pathway to a catabolic or anabolic state.[1]

Anabolic pathways

These pathways require energy (endergonic), are involved in compound synthesis, and are divergent in nature with simple precursors built into large and complex molecules.

Catabolic pathways

These metabolic pathways are involved in the release of energy and most of them are convergent.

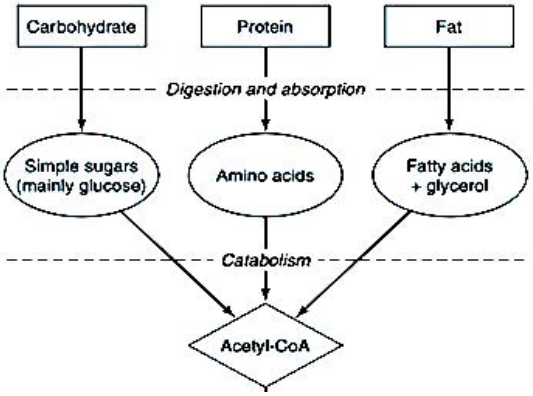


Figure 1: Steps in catabolic processes converging to acetyl-CoA[3]

Major intermediates

The main intermediates of metabolism formed from carbohydrate, protein, and fat catabolism converge at acetyl-CoA (Figure 1).[3]

Other important intermediates of metabolism are pyruvate, succinyl-CoA, and oxaloacetic acid (OAA). Cofactors such as vitamins are required for efficient enzyme functions in metabolic pathways.[3]

Carbohydrate metabolism

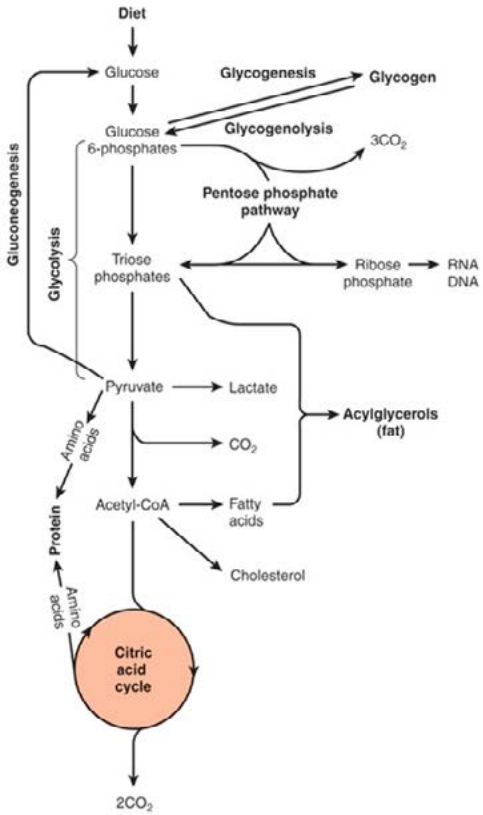
Major dietary carbohydrates in the human diet are polysaccharides (starch, plant storage form of carbohydrate), disaccharides (sucrose, table sugar, and lactose, milk sugar), and monosaccharides (glucose and fructose). Cellular respiration refers to combined reactions that lead to the oxidation of glucose, producing CO_2, H_2O, and ATP.[4] Energy produced per gram of carbohydrates equals 4 kcal/g.

Glycogenesis

The enzyme-mediated conversion of excess glucose to glycogen, a branched polymer of glucose at α-1,4 and α-1,6 links.

Glucose-6-phosphate → glucose-1-phosphate → glycogen

Glycogen is stored in the muscle, liver, and minimally in the brain at 400 g, 100 g, and only 3–12 µmol/g of brain tissue for minute supply, respectively. Glycogen synthetase is the enzyme that initiates glucose conversion to glycogen and is stimulated by high blood glucose levels and insulin.[1,5]



Glycogenolysis

The breakdown of glycogen to glucose in times of glucose deficiency.

Glycogen → glucose-1-phosphate → glucose-6-phosphate

Glycolysis

The conversion of glucose to pyruvate (figure 2a). Pyruvate is further converted to acetyl-CoA under aerobic conditions (presence of oxygen), which is essential for the citric acid cycle. During anaerobic respiration (absence of oxygen), lactate is formed from pyruvate. The other important fate of glucose-6-phosphate is the pentose phosphate pathway producing the ribose-5-phosphate sugar used to make deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) (see figure 2b).

Gluconeogenesis

The pyruvate and citric acid cycle intermediates are converted to glucose from non-carbohydrate precursors, see figure 2a.

Protein metabolism

Proteins are linear chains resulting from AA joined together. Their structures contain approximately 16% nitrogen in addition to carbon, hydrogen, and oxygen. The AA are produced from the digestion of proteins from exogenous and endogenous sources. The complete oxidation of AA produces CO_2, H_2O, and NH_3. The amount of energy produced per gram of protein is 4 kcal. There are essential (these are only obtained from exogenous sources) and non-essential AA (these can be endogenously produced in protein synthesis).[6]

Transamination

Transfer of an amine group from AA to alpha-ketoglutaric acid, thereby transforming it to glutamic acid.

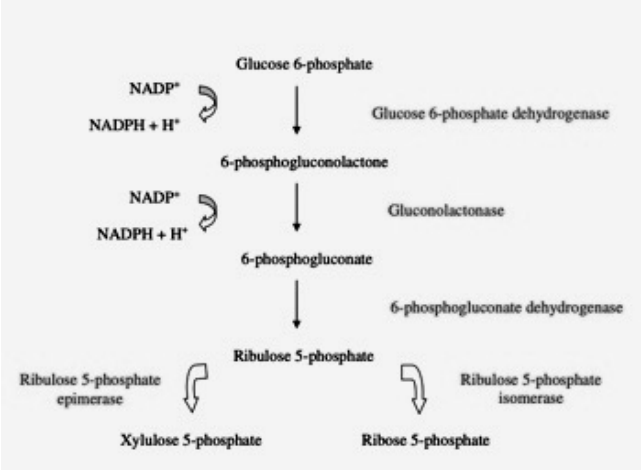


Figure 2a (left), 2b (right): Simplified multiple fates of glucose metabolism and pentose phosphate pathway[3,4]

Oxidative deamination

The removal of an amine group from glutamic acid as ammonia and regenerating alpha-ketoglutaric acid.

Proteolysis

AA can be converted to glucose via gluconeogenesis or may help in the synthesis of non-essential AA. In the liver, NH_3 + HCO_3 + ATP forms carbamoyl phosphate, which is further converted to urea in the urea cycle.[3,6]

Fat metabolism

Fat (triacylglycerol/triglycerides) in the adipose tissue is the largest form of energy reservoir in the body. Other important biological lipids are phospholipids, steroid hormones, and cholesterol. The triglycerides containing no double bonds are called saturated fats compared to unsaturated fats, which contain double bonds. Polyunsaturated fats such as linoleic, linolenic, and arachidonic acids are essential precursors of prostaglandins.[3]

Fats catabolism

Involves complete oxidation of triacylglycerol (TAG) to CO_2, H_2O and heat with 9 kcal/g of energy produced (see figure 4).

Lipolysis

Breakdown of lipids to fatty acids and glycerol.

Beta (β) oxidation

Conversion of fatty acids to acetyl-CoA.

Ketogenesis

Alternative energy production from fatty acids and certain ketogenic AA. Excess acetyl-CoA is converted to acetoacetyl-CoA and further converted to acetoacetate in the liver. The derivatives of acetoacetate are acetone and β-hydroxybutyrate (figure 3 and 4). Commonly formed ketone bodies (figure 3) are acetoacetate, acetone, and β-hydroxybutyrate.[7]

Fats anabolism

Lipogenesis

The formation of lipids from acetyl-CoA and glyceraldehyde phosphate occurs in the cytosol (figure 4). Important cofactors for this process are biotin and nicotinamide adenine dinucleotide (NADPH). Other important fat anabolism pathways lead to cholesterol genesis and subsequent steroidogenesis; all essential for organism survival.

The tricarboxylic acid cycle/Krebs cycle/citric acid cycle

This cycle (figure 5) occurs in the mitochondria and is at the core of energy production, CO_2, and some reduced coenzymes from the acetyl-CoA.[3] Biochemical homeostasis is maintained by mitochondrial influxes and effluxes of intermediates as per cellular needs. The TCA intermediates are used for glucose, AA, fatty acids, and heme synthesis, among others. The other essential efflux of the TCA intermediate is key in the urea cycle.

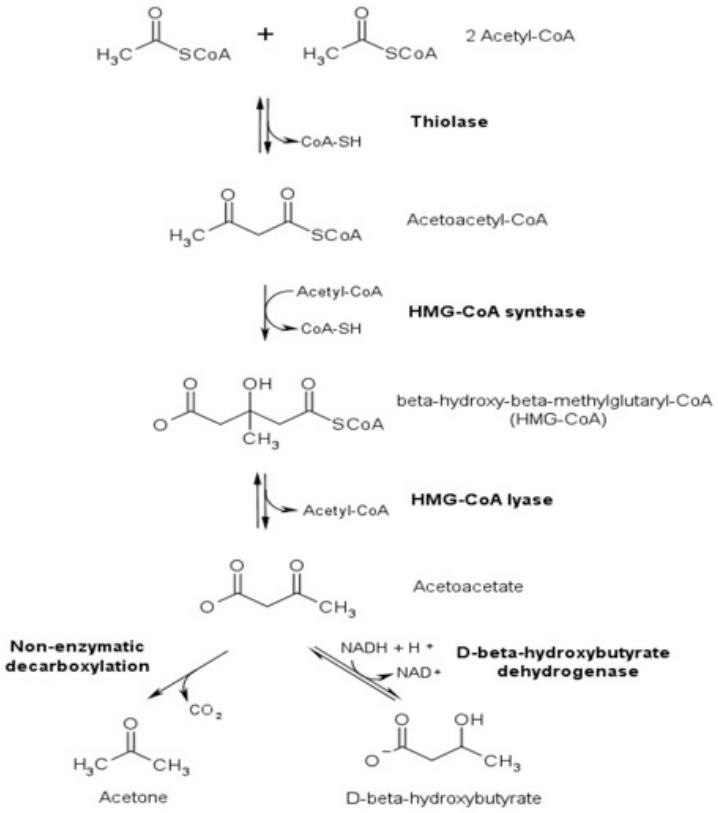


Figure 3: Steps of ketone body production[7]

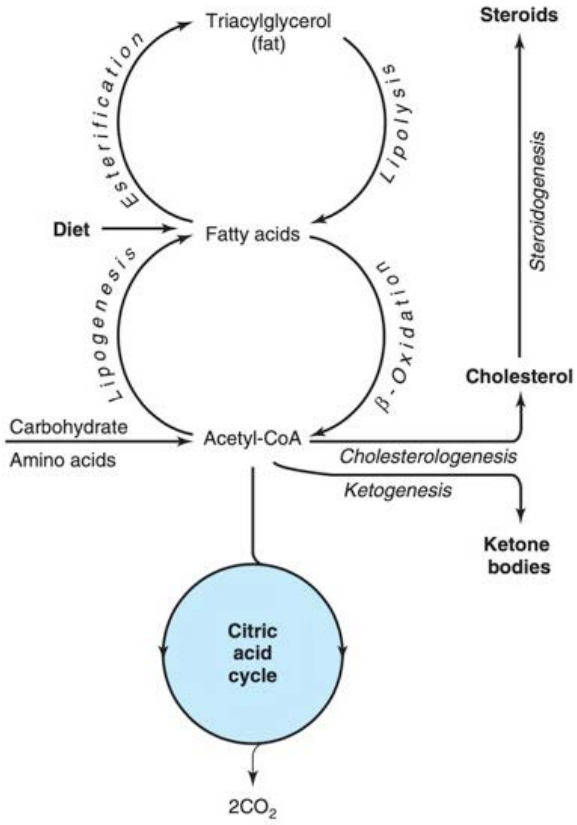


Figure 4: Simplified lipolysis, esterification, lipogenesis, and β-oxidation[3]

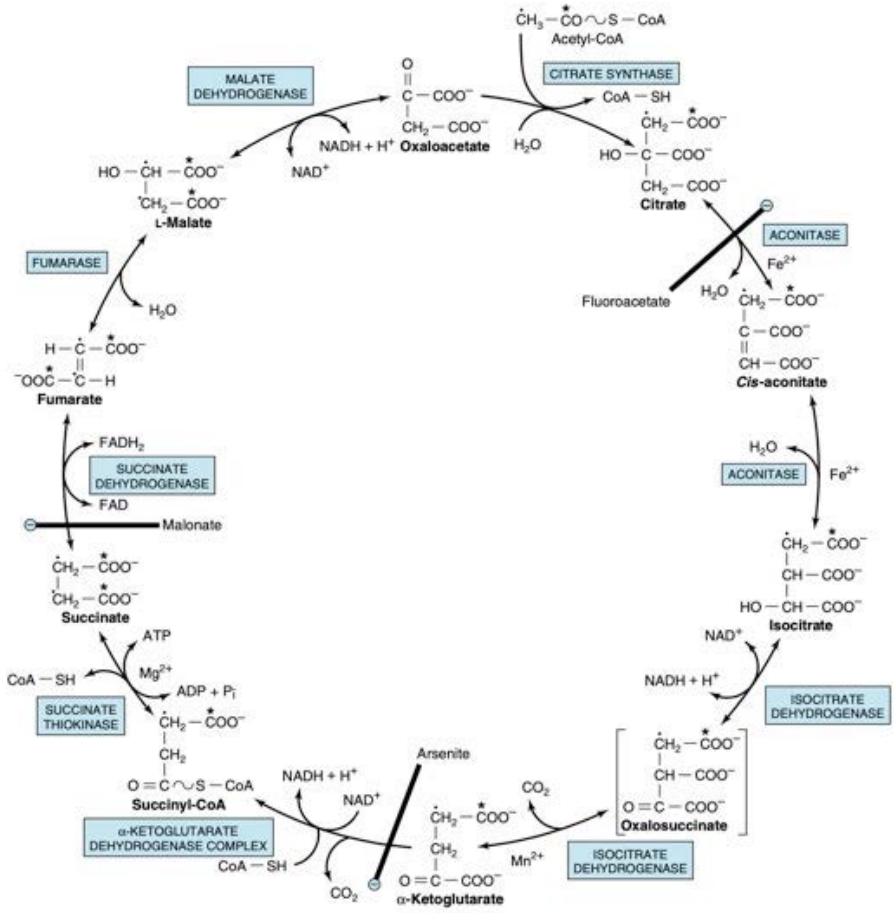


Figure 5: TCA cycle showing the multisteps involved in energy production[3]

Regulation of metabolism

The enzymes involved in all metabolic pathways are regulated by hormones. The hormones either inhibit or stimulate the regulatory enzyme. The enzymatic regulation can be allosteric regulation or covalent modification. The substrate availability, such as citrate levels, fructose-2,6-biphosphate levels, and ATP/AMP ratio, also plays a role in regulating metabolism.[8] Low ATP levels stimulate enzymes of glycolysis, while high ATP levels stimulate TCA enzymes. High citrate levels stimulate acetyl-CoA carboxylase leading to fatty acid biosynthesis. A high level of fructose-1,6-bisphosphate stimulates phosphofructokinase (PFK) of glycolysis and inhibits fructose-1,6-bisphosphates of gluconeogenesis.

Fasting

The prescribed complete voluntary abstinence (nil per os) from caloric intake perioperatively has an impact on intermediary metabolism. During fasting periods, the body lives on reserves. The plasma levels of glucose, AA, and triacylglycerol (TAG) decrease. The insulin secretion declines and glucagon hormone secretion increases to initially stimulate glycogenolysis and later glycolysis, gluconeogenesis, fat oxidation, and ketogenesis take over as fat stores can last longer. The fuel storage in an average 70 kg male is distributed as fats 15 kg, protein 6 kg, and carbohydrates of about 2 kg.

Exercise

During exercise, the body requires added energy production. The cardiovascular system, respiratory system, and endocrine system, among others, need to adjust to meet the increase in intermediate metabolism and energy requirements.

Comorbid diseases

In the context of anaesthesia, there are relevant diseases associated with intermediate metabolism. Perioperatively, the impact on patients with these conditions and knowledge of their metabolic status is necessary for their safe management. Any molecule metabolism (i.e. carbohydrate, protein, lipid, nucleic acid, minerals, and vitamins) can be affected by a disease process.

Other comorbidities, such as hypo/hyper thyroids, lipid storage diseases, hemochromatosis, and sickle cell disease, contribute to intermediate metabolism and may affect the response to anaesthesia.

Diabetes mellitus (DM)

Both type 1 and type 2 DM resulting from insulin deficiency or resistance may lead to abnormal glucose metabolism. Perioperative glycaemic control will affect patient outcomes.

Metabolic syndrome

Obesity resulting from abnormal positive caloric balance may result in complications during anaesthesia, such as difficult airway management and obstructive sleep apnoea.

Inborn errors of metabolism (IEM)

Inherited defects in the activity of an enzyme that affect a wide variety of metabolic processes may result in specific diseases such as galactosemia and phenylketonuria. The pathogenesis is that of either accumulation of toxic precursors, or deficiency in the product of metabolic pathway.

Anaesthesia implications include patient-specific dietary restrictions, fasting time prescriptions, and the risk of triggering these diseases with the associated perioperative stress response.

Glycogen storage diseases

Patients known with this condition are prone to hypoglycaemia during fasting.

Alcoholism

Chronic alcohol use may lead to alcoholic liver diseases, thereby disrupting liver metabolism pathways. Nutrients, toxins, and drugs metabolise abnormal in these patients and therefore require special attention to anaesthetic drug doses.

Cancer cachexia

In advanced cancer, patients develop metabolic abnormalities leading to cachexia, a condition characterised by weight loss and muscle wasting. Patients with this condition may present with a low body mass index and may require preoperative nutritional rehabilitation to improve their metabolic reserves and clinical outcomes.

Intermediate metabolism-relevance in patient investigations

Blood gases

Respiratory quotient (RQ) is the ratio of oxygen consumed versus carbon dioxide produced for the energy yield from nutrients (e.g. for carbohydrates it is 1, lipids 0.7, and protein 0.8). Acid-base disorders, such as acidosis, lead to an increase in RQ while RQ is decreased in alkalosis. Maintaining acid-base balance and optimum temperature is essential for the enzymatic functions involved in intermediate metabolism.

Cardiopulmonary exercise testing (CPET)

CPET is a dynamic test that can identify cardiac or pulmonary disease in patients with borderline abnormal diagnostic tests. Data collected include electrocardiogram (ECG), heart rate, oxygen uptake (essential for aerobic respiration), and carbon dioxide output (major intermediate metabolism biproduct).

Metabolic equivalent of task (METs)

This refers to the amount of oxygen consumed per kilogram per minute. One MET equals 3.5 ml of oxygen/kg/min^{-1}. The higher the METs, the better the patient can tolerate perioperative stress, and hence have a better outcome.[9,10]

Intensive care unit (ICU) feeding

To calculate caloric requirements, basic intermediary metabolism knowledge and the use of indirect calorimetry help meet patient nutritional requirements to improve patient outcomes in this time of stress associated with critical illness.

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References

1. Barrett K, Barman SM, Boitano S, Brooks H. Ganong's review of medical physiology. 25th ed. New York: McGraw-Hill; 2015.
2. Veerappa S, McClure J. Intermediary metabolism. Anaesth Intensive Care Med. 2020;21(3):162-7. https://doi.org/10.1016/j.mpaic.2020.01.003.
3. Murray RK, Granner DK, Mayes PA, Rodwell VW. Harper's illustrated biochemistry. 26th ed. McGraw-Hill Medical; 2003.
4. Adeva-Andany MM, Pérez-Felpete N, Fernández-Fernández C, Donapetry-García C, Pazos-García C. Liver glucose metabolism in humans. Biosci Rep. 2016;36(6):e00416. https://doi.org/10.1042/BSR20160385.
5. Kang Z-Q, Huo J-L, Zhai X-J. Effects of perioperative tight glycemic control on postoperative outcomes: a meta-analysis. Endocr Connect. 2018;7(12):R316-27. https://doi.org/10.1530/EC-18-0231.
6. Schutz Y. Protein turnover, ureagenesis and gluconeogenesis. Int J Vitam Nutr Res. 2011;81(2-3):101-7. https://doi.org/10.1024/0300-9831/a000064.
7. Dhillon KK, Gupta S. Biochemistry, ketogenesis. Treasure Island: StatPearls Publishing; 2023.
8. Guan K-L, Xiong Y. Regulation of intermediary metabolism by protein acetylation. Trends Biochem Sci. 2011;36(2):108-16. https://doi.org/10.1016/j.tibs.2010.09.003.
9. Hennis PJ, Meale PM, Grocott MPW. Cardiopulmonary exercise testing for the evaluation of perioperative risk in non-cardiopulmonary surgery. Postgrad Med J. 2011;87(1030):550-7. https://doi.org/10.1136/pgmj.2010.107185.
10. Nawoor-Quinn Z, Oliver A, Raobaikady R, et al. The Marsden Morbidity Index: the derivation and validation of a simple risk index scoring system using cardiopulmonary exercise testing variables to predict morbidity in high-risk patients having major cancer surgery. Perioper Med (Lond). 2022;11(1):48. https://doi.org/10.1186/s13741-022-00279-8.

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Sodium

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Sodium is a major extracellular cation. It is a significant determinant of the osmolality of the plasma. Human cells are bathed in salty water, so the osmolality must be regulated. The primary cause of dysnatraemias (abnormal sodium concentrations), hyper- and hypo-, is caused by the imbalance of electrolyte-free fluid intake and loss.[1] Clinicians must look at correcting the fluid abnormality instead of focusing on serum sodium. Dysnatraemias are a significant cause of morbidity in intensive care unit (ICU) patients, with an incidence of up to 27% in ICU patients compared to 0.2% in general ward patients.[2,3]

Keywords: sodium, extracellular cation, osmolality

Relationship of plasma sodium, electrolytes, and water content

Osmolality is the concentration of osmoles dissolved per kilogram of plasma water. Osmolarity is the concentration of osmoles per litre of plasma water. Osmolality is the preferred term since it can be measured with an osmometer.[1] Tonicity is the concentration of moles (effective osmoles) that do not cross cell membranes.[1] The accumulation of effective osmoles drives the movement of water. Therefore, hypotonic plasma drives water movement intracellularly, causing the cells to swell, while hypertonicity drives water out of the cells, causing them to shrink.[1,4]

Sodium and glucose, in the absence of insulin, act as effective osmoles and contribute to both osmolality and tonicity.[1] Since it permeates membranes, urea contributes to osmolality without affecting tonicity.[1] Therefore, the extracellular fluid regulates the body's solute and sodium. The body has mechanisms to maintain the tonicity of the plasma close to an acceptable level. The regulatory mechanism keeps the sodium level within its normal range (135–145 mmol/L).

The solute content in extracellular and intracellular is the same. The difference in osmolality between intracellular and extracellular is the same. Aquaporins on cellular membranes allow the free movement of water to balance osmolality, while the Na+/K+ ATPase keeps the sodium outside the cells. Though sodium is extracellular, and potassium is an intracellular cation, body fluid can be considered a large bath containing sodium, potassium, and water. Edelman's equation expressed this relationship: Plasma sodium is directly proportional to the sum of exchangeable sodium and potassium and inversely proportional to extracellular fluid.[4,5]

A substantial amount of sodium is bound to proteoglycan, the building block of connective tissue, cartilage, and bone.[5] The concentration of sodium in cartilage is twice that of plasma. This high sodium concentration allows the cartilage to hold water and withstand pressures exceeding 20,000 mmHg during exercise.[5,6]

Proteoglycan in the skin is a sodium reservoir, and the number of negative charges on its surface is related to the sodium concentration in the interstitial fluid.[5] In rat experiments, rats with chronic hyponatraemia experienced osteopenia more than those with vitamin D deficiency.[5] Sodium loss from the bone exceeded the calcium loss.[5] Osteoclast activity increases from the direct sodium effect and possibly vasopressin.[5] In humans, chronic hyponatraemia causes osteoporosis and recurrent fractures.[1,5] During extreme endurance exercises, bone density decreases remarkably due to changes in plasma sodium resulting from the nonosmotic release of antidiuretic hormone (ADH) from pain and stress and the resultant hyponatraemia.[1,5]

Plasma sodium concentration and tonicity balance

Plasma sodium and blood-brain barrier

Sodium readily crosses the systemic endothelial membrane through the clefts between endothelial cells, resulting in a similar sodium concentration between the plasma and the interstitial fluids.[1,5] There is a slight difference attributed to the concentration of albumin. However, the brain has tight endothelial junctions lined by astrocytic foot processes, creating a blood-brain barrier, thereby preventing sodium from crossing the barrier. Abnormal plasma sodium causes water to enter or leave the brain, leading to swelling or shrinkage of the brain.[5]

Regulation of plasma sodium and extracellular fluid osmolarity

A feedback system regulates the plasma osmolality and sodium concentration. When the osmolality of body fluid is high, the volume receptors are responsible for thirst and ADH secretion.[1,5] The true osmoreceptors are hypothalamic neurons expressing transient receptor potential cation channel subfamily vanilloid

member 1 and member 4 (TRPV1 and TRPV4). TRPV1 responds to capsaicin, a vanilloid which results in a burning sensation associated with ingesting chillies.[5] The polymorphism of TRPV4 has been identified in humans in average ageing men and can result in mild hyponatraemia compared to those without the polymorphism.[5] The ADH is synthesised in the hypothalamus as a prohormone, thereafter cleaved and stored as ADH in the posterior pituitary.[1] Hypertonicity causes shrinkage of the osmoreceptors, which causes subsequent depolarisation and release of ADH from the posterior pituitary.[1]

Healthy individuals' thirst and vasopressin secretion are suppressed when sodium concentrations are below 135 mmol/L, while it continues to rise with increasing sodium levels above 135 mmol/L.[5] It may also be secreted in response to circulatory inadequateness (hypovolemia), inappropriately like in the syndrome of inappropriate ADH secretion (SIADH), and can be secreted ectopically with no haemodynamic stimulus or osmotic stimulus.[1,5,7]

Renal action of antidiuretic hormone

The site of action of the ADH is the renal collecting ducts, where it exerts its effects by binding onto the V2 receptors in the collecting ducts.[1,5] Without ADH, the collecting ducts are impervious to water, producing dilute urine.[1,5] Once ADH is bound, the aquaporins are inserted into the collecting ducts, allowing the water to seep towards the hypertonic renal medulla.[1] When the sodium concentration is 145 mmol/L, the level of vasopressin is highest, producing maximally concentrated urine of about 1 200 mOsm per kilogram.[1,5] The presence of dilute urine in the face of high sodium indicates vasopressin deficiency, nephrogenic or neurogenic diabetes insipidus.[5,6] In the conscious patient with a total deficiency of vasopressin or resistance of the renal tubules to respond to the effects of vasopressin, hypernatraemia doesn't develop because the thirst mechanism remains intact.[1,5,6] Hypernatraemia only develops in patients who are too sick, unconscious, young, or old.[2,5,8]

Maximal dilution of urine also prevents hyponatraemia, except if water intake is excessive.[1] Hypotonic hyponatraemia occurs when there is a problem in the renal tubules to produce dilute urine, as in patients taking diuretics.[1,5,7] By inhibiting sodium reabsorption in the loop of Henle, loop diuretics reduce renal medullary hypertonicity and hence reduce water reabsorption in the collecting ducts.[1] Compared to thiazide diuretics, they reduce renal concentrating ability and can contribute to hypernatraemia.[1]

Hyponatraemia

The severity of symptoms depends on the rate of onset. Hyponatraemia is a sodium concentration less than 135 mmol/L, and severe hyponatraemia is below 120 mmol/L.[1,2,5,7] Hyponatraemia can occur at low, normal, or elevated tonicity. The cells swell up as hyponatraemia develops. The brain experiences more significant stress in a fixed cranium.[1,5] Hypotonicity can lead to cell membrane rupture from swelling. With time, cells adapt and protect their survival by adjusting their intracellular content.[1,5] Organic osmolytes are intracellular molecules like taurine, glutamate, and myo-inositol found naturally in cells.[5] With hypotonicity, they are released from the cells through volume-leak pathways.[1,5]

The symptoms are limited to the brain, though all cells are affected by hyponatraemia. Severe and permanent neurologic fallout may occur.[1,3,5,7] Astrocytes are more sensitive to the osmotic stress.[1,5] To mitigate the swelling from hypotonicity, the expulsion of potassium and other electrolytes occurs over 6–12 hours, and the organic osmoles over 24–48 hours.[1,5]

Acute hyponatraemia of fewer than 48 hours, meaning the cells did not have time to adjust as above, is uncommon.[1] There are a few cases of acute hyponatraemia, like ingestion of salt as a suicide attempt, following strenuous physical exercise, and ingestion of 3,4-methylenedioxymethamphetamine (MDMA).[1] All other cases must be treated as chronic hyponatraemia.[1,5]

The symptoms progress from mild nausea, vomiting, and headaches to severe symptoms like seizures, coma, cerebral oedema, and neurogenic pulmonary oedema.[1,5,7] Caution must be applied while correcting hyponatraemia. The foot processes of astrocytes, which encircle the neurons and capillaries, express aquaporins that allow the water to cross the blood-brain barrier.[5] Cell-cell transfer of taurine allows neuronal cells to maintain their volume while astrocytes swell up.[5] After 24–48 hours, through the loss of organic osmoles, astrocytes retain their volume but are vulnerable to the hypertonic stress associated with acute sodium replacement.[5] The astrocytes take a week to regain their organic osmoles.[5] Hypertonicity at this stage caused by rapid correction can damage astrocytes, triggering apoptosis, disruption of the blood-brain barrier, and demyelination.[1,5]

Pseudohyponatraemia is due to laboratory error in the measurement of sodium in the presence of high lipids and paraproteins. In this situation, hyponatraemia will be accompanied by normal osmolality.[1,7]

Hyponatraemia with high osmolality is seen in the presence of hyperglycaemia. The glucose draws the water from the cells into the extracellular space due to the high osmolality. This is called translocational hyponatraemia.[1,7] Sodium decreases by about 1.6 mEq/L for every 100 mg/dl increase in glucose.[1,7]

Hypotonic hyponatraemia requires investigations to find the cause, as discussed below.

Hyponatraemia and urinary dilution

Hyponatraemia and low urinary osmolality of less than 100 mOsm/kg of water indicate maximally suppressed ADH, which is the expected response.[1,5,7] The problem may indicate the administration of electrolyte-free water, which exceeds the renal excretion of water.[5] In a standard Western diet, a solute load of about 800 mOsm is generated and excreted daily. If urine can be maximally diluted to 50 mOsm/kg of water, this corresponds to clearance of 16 L electrolyte-free water.[1,5] Hyponatraemia in

this scenario may occur from primary polydipsia, ingesting less solute load like tea and toast, or excessive beer drinking.[1,5,7]

The most typical cause of hypotonic hyponatraemia is ADH deficiency, which results in the inability to dilute the urine.[1,5] The patient may be euvolemic (common cause SIADH), hypovolemic (e.g. haemorrhage and mineralocorticoid deficiency), and hypervolemic (e.g. cardiac and liver failure).[1,5,7]

Treatment of hypotonic hyponatraemia

The most significant risk in treating hypotonic hyponatraemia is an osmotic demyelinating syndrome (ODS), when sodium is replaced rapidly in chronic hyponatraemia.[1,5] The risk of ODS in acute hyponatraemia is negligible since the brain has not adjusted to low sodium.[1]

Chronic hyponatraemia with a sodium concentration of less than 105 mEq/L is associated with alcoholism, and cirrhosis carries a higher risk of ODS.[1] Hypokalaemia may increase the risk of ODS as potassium is exchanged for sodium.[5]

Acute hyponatraemia may be corrected quickly using hypertonic saline over 4–6 hours. Thereafter, 1–2 ml/kg/hour boluses to increase the sodium concentration by 4–6 ml.[1,5] In chronic severe hyponatraemia, the aim is to increase sodium by 8 mEq/L in 24 hours in the presence of severe symptoms like seizures; hypertonic saline boluses can be given as above to abolish the seizures and desmopressin can be considered at the dose of 2 mcg every 4–6 hours.[1,5,7] If the patient has mild to moderate symptoms, the aim is to increase sodium by 10–12 mEq/L over 24 hours.[1,6] With mild to moderate cases, treatment should be according to underlying conditions.

Pharmacological treatment with vaptans, an ADH antagonist, can treat euvolemic and hypervolemic hyponatraemia.[5,7]

Hypernatraemia is defined as a sodium concentration greater than 145 mmol/L. Using the Edelman equation, it can occur due to additional sodium added or the loss of extracellular fluid. It is always associated with hypertonicity.[2,5,7] Water loss is the common cause. Small increases in tonicity stimulate ADH secretion and the thirst mechanism.[1,5,7] The patients at risk are those of advanced age with reduced levels of consciousness and infirmity.[7,8]

Most patients admitted to the hospital with hypernatraemia were the elderly from old age homes, and the causes ranged from physical disabilities, which limited their ability to access water, and urinary incontinence, which made them limit their fluid intake.[1,8] Most old people are on polypharmacy, including diuretics, which may increase renal losses, and they have a reduced thirst mechanism compared to younger people.[8] hormonal changes can contribute to hypernatraemia, such as reduced renin-angiotensin-aldosterone system (RAAS), reduced aldosterone, reduced ADH, and increased atrial natriuretic peptide (ANP).[8]

An unusual cause is a tumour in the hypothalamus, leading to the inability to perceive thirst; this is called primary hypernatraemia.[1]

Causes are divided into:[1,7]

- Inadequate water intake: intubated, elderly, and reduced levels of consciousness.
- Extrarenal hypotonic losses: gastrointestinal tract (GIT) losses and sweat.
- Renal concentrating abilities: loop and osmotic diuretics and central and nephrogenic diabetes insipidus.
- Excessive salt intake: hypertonic fluid administration, like hypertonic saline, and total parenteral nutrition (TPN).

Treatment

Treat the underlying causes like diarrhoea or long-term desmopressin administration for central diabetes insipidus.

There is no consensus on the correction rate of hypernatraemia like in hyponatraemia.[1,5] Acute onset can be corrected rapidly within 24 hours. For chronic hypernatraemia, it is suggested to reduce sodium by about 0.5–1 mEq/L every hour with the aim of correcting sodium in 48 hours.[1,5,7]

Conclusion

Abnormal sodium concentration can lead to morbidity and mortality. The neurons are affected more than other cells, with mild or severe symptoms depending on the sodium level. The correction must also be carried out cautiously, as rapid correction may cause more harm than good.

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References

1. Seay NW, Lehrich RW, Greenberg A. Diagnosis and management of disorders of body tonicity-hyponatremia and hypernatremia: core curriculum 2020. Am J Kidney Dis. 2020;75(2):272-86. https://doi.org/10.1053/j.ajkd.2019.07.014.
2. Chand R, Chand R, Goldfarb DS. Hypernatremia in the intensive care unit. Curr Opin Nephrol Hypertens. 2022;31(2):199-204. https://doi.org/10.1097/MNH.0000000000000773.
3. Sim JK, Ko R-E, Na SJ, Suh GY, Jeon K. Intensive care unit-acquired hyponatremia in critically ill medical patients. J Transl Med. 2020;18(2). https://doi.org/10.1186/s12967-020-02443-4.
4. Tinawi M. Hyponatremia and hypernatremia: a practical guide to disorders of water balance. Arch Intern Med Res. 2020;3(1):74-95. https://doi.org/10.26502/aimr.0025.
5. Sterns RH. Disorders of plasma sodium-causes, consequences, and correction. N Engl J Med. 2015;372(1):55-65. https://doi.org/10.1056/NEJMra1404489.
6. Almond CSD, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the Boston Marathon. N Engl J Med. 2005;352(15):1550-6. https://doi.org/10.1056/NEJMoa043901.
7. Braun MM, Barstow CH, Pyzocha NJ. Diagnosis and management of sodium disorders: hyponatremia and hypernatremia. Am Fam Physician. 2015;91(5):299-307.
8. Morley JE. Dehydration, hypernatremia, and hyponatremia. Clin Geriatr Med. 82015;31(3):389-99. https://doi.org/10.1016/j.cger.2015.04.007.

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FCA REFRESHER COURSE

Work, energy, and power

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Introduction

Mechanics is a section of physics that describes energy and forces and their effect on the motion of bodies.[1] Work, energy, and power are three principles described in mechanics. These three principles are applicable in physiology, as seen in respiration and cardiac output.

Definitions

Work: Work is done when a force applied to an object causes displacement in the same direction as the force.[2] Work (J) = force (N) × distance (m).

Energy: The capacity to do work; measured in joules (J).[3]

Power: The rate at which work is done; measured in watts (W).[4] Power = work (J) / time (seconds).

Work

Work is done when a force applied to an object causes displacement in the same direction as the force.[2] If an object is not displaced despite a force being applied to it, no work is done. The three main components of work include force, displacement, and cause.[3] The SI unit for work is the joule (J), defined as "one joule of work is done when a force of one newton moves its point of application one metre in the direction of the force".[4] One joule is therefore equal to one newton metre. The equation for work is force multiplied by distance (Figure 1).[4]

The equation for work can be modified to be the product of pressure and volume. This is applicable in respiratory physiology to calculate the work of breathing and in cardiac physiology to calculate the work done by the heart.[6] This is done in the following way:

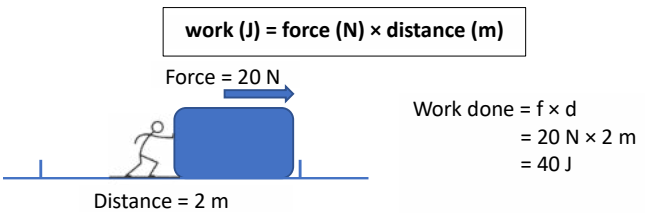

Figure 1: Work done when a force causes a displacement[3]

- pressure = force / area

Therefore:

- force = pressure × area

But:

- work = force × displacement

Therefore:

- work = pressure × area × displacement

However:

- volume = area × displacement

Therefore:

- work = pressure × volume (work = $\Delta P \times \Delta V$)

Energy

Energy is defined as the capacity to do work, measured in joules (J). Energy is essential for work to be performed and is equivalent to work.[3] The conservation of energy principle states that energy cannot be created or destroyed, only transformed from one state to another. Energy exists in many forms and is interchangeable. Mechanical energy exists as either kinetic or potential energy (Figure 2). An object in motion has kinetic energy, which is measured in joules. The energy stored by an object due to its position is potential energy.[3]

mechanical energy = kinetic energy + potential energy

kinetic energy (E_K) = ½ m × v²

m = mass (kg)

v = velocity ($m.s^{-1}$)

gravitational potential energy (Ep) = m × g × h

m = mass (kg)

g = gravity (9.8 ms^{-2} or 9.8 $N.kg^{-1}$)

h = height (metre)

Figure 2: Calculations for energy

power = work (J) / time (seconds)

However:

- work = force × displacement and velocity = displacement / time
- power = force × distance / time

Therefore:

- power = force × velocity

Figure 3: Calculations for power

Power

Power is defined as the rate at which work is done. It is measured in watts (W).[4] One watt is one joule per second.[6] Power describes the time taken for a force to cause displacement.[3] The equation for power is work divided by time. Since velocity is described as displacement over time, it is possible to describe power as force multiplied by velocity (Figure 3).

Clinical application of work, energy, and power

Respiration

Work of breathing

For the lung and chest wall to move, work needs to be done. During respiration, work is required to overcome elastic forces or elastic recoil from the lungs and chest wall, as well as the airway and tissue resistance. Resistive forces include the airway, tissue, and viscous resistance to airflow.[3,7] In a spontaneously breathing patient, work is performed during inspiration by the respiratory muscles, and by the ventilator in a ventilated patient.

Work done on the lung can be measured using airway pressure and volume change. This is easier to measure in a ventilated patient than in a spontaneously breathing patient.[7] The pressure-volume curve (Figure 4) is used to demonstrate the work of the lung. The striped area indicates work done to overcome the elastic forces, and the dotted area indicates viscous and tissue resistance. The total work done on the lung is the combined striped and dotted areas. An increase in tidal volume will result in an increased elastic work area, whereas an increase in respiratory rate or flow rate will increase the viscous work area.[8]

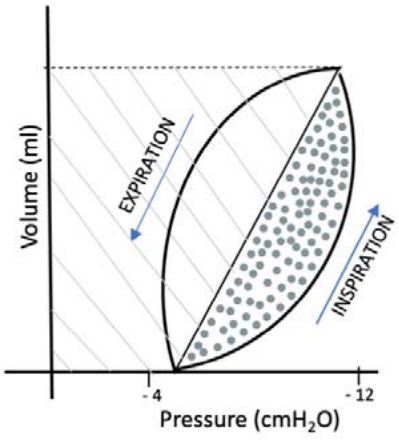

Figure 4: A pressure-volume curve showing work done on the lung during respiration[8]

The total work of breathing is more difficult to measure. It can either be measured by calculating the oxygen cost of breathing (the difference between the total body oxygen uptake [VO_2] in controlled ventilation and the VO_2 with spontaneous ventilation), or by measuring the mechanical work of breathing. Oesophageal pressure (P_{ES}) is used as a reflection of intrapleural pressure, and airway pressure (P_{AW}) is measured. Transpulmonary pressure is then calculated as the difference between the two pressures. P_{AW} represents the work done on the lungs, chest wall, and respiratory apparatus, while transpulmonary pressure is the work done on the lungs only, and transthoracic pressure represents work done on the chest wall (atmospheric pressure minus intrapleural pressure).[7] In a spontaneously breathing patient it is difficult to measure the work of the chest wall.

Expiration is a passive process, but it still requires energy to overcome airway and tissue resistance. Potential energy created by the distention of elastic elements is stored in the chest wall during inspiration and used during expiration.[7,8]

The work of breathing is increased in obstructive lung disease due to an increase in airway resistance. It is also increased in mechanical ventilation due to the use of equipment, such as endotracheal tubes, valves in the circuit, and tubing.[5] Calculating the work of breathing in critically ill patients can assist with weaning ventilator support and guide the timing of extubation.[7]

Energy

During inspiration, mechanical energy is used to overcome elastic and resistive forces. The work done to overcome elastic forces of the lungs and chest wall is stored as potential energy. This potential energy is used for the work of expiration.[3,6,8] The work done to overcome resistive forces is converted to heat energy. An increase in airway resistance or respiratory rate can result in energy requirements that exceed the stored potential energy. Expiration then becomes an active process and expiratory muscles are used.[3]

Power

The type of flow affects the power of breathing. Turbulent flow results in a larger pressure gradient than laminar flow. In laminar flow, pressure is proportional to flow, whereas in turbulent flow, pressure is proportional to the square of flow. When a patient is hyperventilated, the flow becomes turbulent and therefore power increases.[6]

Cardiac

Work of myocardial contraction

As for respiration, the change in volume and pressure can be used to calculate work for each ventricle. Cardiac pressure-volume curves can be used to determine the work of myocardial

contractions. Pressure in the left ventricle can be measured using an intraventricular cardiac catheter, and volume can be assessed using echocardiography. Mean arterial pressure and cardiac output are directly proportional to the work of the heart. Therefore, increased cardiac output and hypertension result in increased work of the heart and energy demand.[6]

Power of the heart

The power of the myocardium can be calculated by dividing work by the heart rate. The power of the heart can also be calculated as the product of fluid flow (cardiac output) and pressure difference. The power of the left side of the heart can be calculated using the mean arterial pressure minus the pulmonary venous pressure (in Pa) multiplied by the cardiac output (in m^3s^{-1}). To calculate the power of the right side of the heart, the mean pulmonary artery pressure minus the central venous pressure (in Pa) is multiplied by the cardiac output (in m^3s^{-1}).[6]

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References

1. Merriam-Webster Dictionary. Mechanics definition. Available from: https://www.merriam-webster.com/dictionary/mechanics.
2. Kalsi A, Balani N. Physics for the anaesthetic viva. Cambridge: Cambridge University Press; 2016. p. 9-10. https://doi.org/10.1017/CBO9781316181515.
3. Wilson M. Mechanics: force, mass, acceleration energy, work, power. Anaesth Intensive Care Med. 2020;21(5):256-60. https://doi.org/10.1016/j.mpaic.2020.02.007.
4. Cross ME, Plunkett EVE. Physics, pharmacology and physiology for anaesthetists: key concepts for the FRCA. Cambridge: Cambridge University Press; 2008. p. 21-2. https://doi.org/10.1017/CBO9780511544538.
5. Hill DW. Physics applied to anaesthesia II: mechanics. Brit J Anaesth. 1965;37:710-3. https://doi.org/10.1093/bja/37.9.710.
6. Davis PD, Kenny GNC. Basic physics and measurement in anaesthesia. 5th ed. London: Butterworth-Heinemann; 2003. p. 87-95.
7. French CJ. Work of breathing measurement in the critically ill patient. Anaesth Intensive Care. 1999;27(6):561-73. https://doi.org/10.1177/0310057X9902700602.
8. West JB, Luks AM. West's respiratory physiology: the essentials. 10th ed. Philadelphia: Wolters Kluwer; 2016. p. 134-5.

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Drug action on the myometrium

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Introduction

The mechanisms responsible for uterine contraction have been extensively explored. A reasonable insight into these mechanisms is required to understand the pharmacology of drugs that induce and maintain uterine contraction (uterotonics) and relax the uterus (tocolytics). Both the uterotonic and tocolytic drugs are used extensively in current obstetric practice and the associated side effects are not uncommon. Some of our anaesthetic drugs also act on the myometrium.

Overview of uterine contraction and relaxation

Spontaneous changes in the electrical activity of myometrial cells (mechanism unknown) induce membrane depolarisation, which opens voltage-gated L-type calcium channels and allows the influx of calcium into the cytosol. The calcium binds to calmodulin and activates myosin light-chain kinase (MLCK). The resultant ATP-dependent phosphorylation of myosin light chains allows the interaction of myosin and actin, cross-bridge formation, and force development.[1–3] This entire process is depicted in Figure 1.

Myosin light-chain phosphatase (MLCP) dephosphorylates myosin, thereby reducing myosin ATPase activity and muscle tension. The opposing effects (phosphorylation versus dephosphorylation of myosin) of MLCK and MLCP are dependent on the intracellular calcium concentration. The myometrial smooth muscle relaxes when the intracellular calcium concentration decreases due to calcium extrusion from the cell or sarcoplasmic uptake. This reduces MLCK activity and allows the dephosphorylation of myosin by MLCP.[1,2]

The regulation of these pathways is complex and not completely understood. Several second-messenger systems are involved and provide further potential targets for drugs. Various prostaglandins (PGs) also exert their effect on the myometrium. Each of these PGs binds to its specific G-protein-coupled receptor.[1,2] The mechanisms of the different PGs will be explored later. Furthermore, gap junctions between individual myometrial smooth muscle cells allow coordinated uterine contraction.[2]

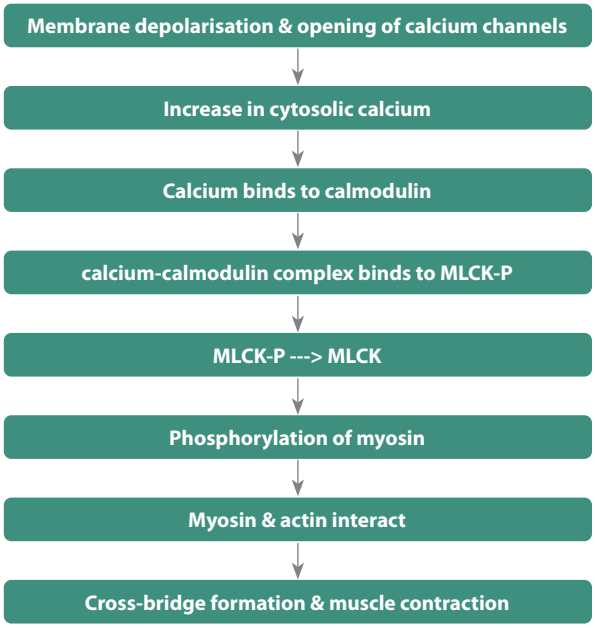

Figure 1: Uterine smooth muscle contraction process
MLCK – myosin light-chain kinase, MLCK-P – phosphorylated (inactive) MLCK

Relevant physiological changes during pregnancy and labour

The expression of myometrial oxytocin receptors (OXTRs) is upregulated significantly and progressively during pregnancy and the number and concentration of these receptors peak during early labour. In contrast, the release of oxytocin does not change during pregnancy and early labour. However, an increase in oxytocin release does occur during the crowning of the fetal head and lasts until the delivery of the placenta.[1]

PG production gradually increases during the first stage of labour, followed by a more rapid increase during the second stage, and a peak at the time of delivery of the placenta.[1] Pregnancy is also associated with an increase in myometrial gap junctions.[3,4]

Uterotonics

Indications for the use of uterotonics are:

1. induction of labour or termination of pregnancy;
2. augmentation of slowly progressing labour;

3. promoting the delivery of the placenta; and

4. reducing postpartum bleeding.[2]

Oxytocin

Oxytocin is a nonapeptide hormone naturally released in pulses from the posterior pituitary gland and is structurally similar to vasopressin. The synthetic form of oxytocin is the drug syntocinon.[2]

Oxytocin is usually administered intravenously as it is inactivated in the stomach. It does not bind to plasma proteins and is metabolised by the kidneys and liver, with a circulating half-life of 10–15 minutes.[5]

The OXTR is a G-protein-coupled receptor with seven transmembrane domains. Binding of oxytocin to its receptor results in the production of inositol triphosphate (IP3) and diacylglycerol (DAG) via the effect of phospholipase C (PLC) on phosphatidylinositol bisphosphate (PIP2). IP3 triggers the release of calcium from the sarcoplasmic reticulum (SR). The calcium then binds to calmodulin and initiates the myometrial contraction pathway as described earlier. DAG stimulates PG synthesis. Oxytocin also activates and increases cyclooxygenase (COX) 2, resulting in further PG production.[1–3]

Other mechanisms of action of oxytocin include the inhibition of MLCP, inhibition of calcium efflux from the cytoplasm, and stimulation of nitric oxide (NO) production. OXTRs are also present in vascular and renal endothelium, as well as cardiac myocytes. It has been proposed that the release of NO mediates the vasodilatation and natriuresis commonly seen after oxytocin administration.[1]

Other than myometrial contraction, oxytocin has several other physiological effects and influences the cardiovascular system, maternal and sexual behaviour, and memory formation.[3]

Oxytocin has a narrow therapeutic range and is associated with significant cardiovascular side effects. Peripheral vasodilatation, hypotension, and increased cardiac output are common. The cardiac output is increased by an increase of both heart rate and stroke volume and has a protective effect in most patients. Hypotension is likely due to NO-induced vascular smooth muscle relaxation. At relatively large bolus doses (10 IU), myocardial ischaemia may occur and pulmonary artery pressures may be increased. These changes may cause considerable cardiovascular instability in patients who cannot increase their cardiac output, such as those who are hypovolaemic, have reduced ventricular function, or have stenotic lesions of their mitral or aortic valves.[3,6]

A moderate antidiuretic effect is attributed to oxytocin's structural similarity to vasopressin. In excessive doses, oxytocin may cause water retention and hyponatraemia. Non-cardiovascular side effects of oxytocin include nausea, vomiting, flushing, and headaches.[3,4]

The administration of oxytocin during augmentation of labour may increase the risk of uterine hyperstimulation and fetal distress. Placental perfusion may be reduced when uterine blood vessels are occluded by an excessively contracted myometrium.[2]

OXTR desensitisation is a concern when oxytocin is infused during induction or augmentation of labour. The ED90 in oxytocin-naïve patients during caesarean delivery is 0.35 IU, but after oxytocin augmentation, the ED90 is 3.0 IU. Repeated doses or prolonged infusions of oxytocin seem to decrease its clinical effectiveness, and second-line uterotonics should be considered in these patients. There is also some evidence suggesting that the haemodynamic response to a second dose of oxytocin is less.[3,6]

Carbetocin

Carbetocin (1-desamino-1-monocarbo-[2-O-methyltyrosine]-oxytocin) is a long-acting synthetic oxytocin analogue with a half-life of 50 minutes. It binds exclusively to OXTR in the myometrium and stimulates rhythmic contractions, increases the frequency of contractions, and increases uterine tone. Uterine contraction is produced two minutes after administration, irrespective of route. The rhythmic contractions persist for 60 minutes after intravenous injection (IVI) and 120 minutes after intramuscular injection (IMI).[1,3]

Carbetocin is currently only registered for the management of post-partum uterine atony. The side effect profile is similar to oxytocin and similar haemodynamic effects should be expected. Contraindications include hepatic, renal, and severe cardiovascular disease, epilepsy, as well as preeclampsia and eclampsia.[1,3]

Ergot alkaloids

Ergot is derived from the fungus *Claviceps purpurea*.[3] Ergometrine is an ergot alkaloid, which when administered as ergometrine maleate or methylergometrine causes rapid tonic contraction of the uterus. It is therefore contraindicated for use in labour but is a second-line agent for postpartum haemorrhage (PPH) prevention.[3,4]

Ergometrine can be administered as an IMI or slow IVI at dosages of 0.1 to 0.5 mg. The onset of action is very rapid after IVI and within 1–5 minutes after IMI. It is metabolised by the liver and the half-life is 120 minutes.[3,4]

The exact mechanism of action is unclear but involves the influx of calcium into the myometrial cells. Proposed binding sites include calcium channels as well as α-receptors. Ergometrine also has an affinity for 5-hydroxytryptamine 1, noradrenaline, and dopamine receptors throughout the body.[1,3]

Side effects include systemic and pulmonary vasoconstriction and ergometrine is therefore contraindicated in preeclampsia, eclampsia, hypertension, and cardiac disease. A 0.5 mg dose results in a high incidence of nausea and vomiting.[3,4,6]

Syntometrine

Syntometrine is a 1 ml mixture of 0.5 mg ergometrine and 5 IU oxytocin. It is usually administered as IMI for the active management of the third stage of labour and the prevention of PPH, but may also be administered as a slow IVI for the management of severe PPH. The combination of the two drugs ensures a rapid onset of action and a sustained duration of action. The side effect profile is the same as for oxytocin and ergometrine and the contraindications are also the same.[1,3]

PGs

PGs are products of the arachidonic acid pathway and bind to their respective G-protein-coupled receptors. PGs E1, E3, F and T are thought to cause contractile responses, whereas PGs D, E2, E4 and I cause relaxation.[2]

The concentrations of PGF2α and PGE increase naturally during late pregnancy and enhance myometrial contraction, mainly by increasing the intracellular calcium concentration. PGF2α increases intracellular calcium by stimulating IP3-mediated SR calcium release, increasing the frequency of membrane action potentials and activating non-specific cation channels. The exact mechanism of PGE is unclear.[2]

Due to the very short half-life of the naturally occurring PGs, PG analogues were developed. Misoprostol, the synthetic analogue of PGE1, can be administered orally, sublingually, rectally, or vaginally. It does not need to be refrigerated during storage, unlike most other uterotonics. Misoprostol indications include termination of pregnancy, incomplete miscarriage, induction of labour (unfavourable cervix), and PPH. The PGs are more effective than oxytocin for the termination of pregnancy as the expression of OXTRs only increases during the third trimester.[1,2]

Dinoprostone, a PGE2 analogue, is usually administered as a gel to promote cervical ripening or to induce labour.[2,4] Intramyometrial PGF2α is a second-line agent for atonic PPH but is associated with severe side effects such as bronchospasm and ventilation-perfusion mismatch. IVI use is contraindicated. Other common side effects of synthetic PGs are hyperpyrexia, diarrhoea, nausea, and vomiting.[1,3,4,6]

Antiprogestins

Progesterone inhibits uterine contraction throughout pregnancy and maintains uterine quiescence (see tocolytics below). Antiprogestins, such as mifepristone, antagonise progesterone and indications include induction of labour and termination of pregnancy.[2]

Tocolytics

Once preterm labour is initiated, it progresses via the same mechanisms as term labour. Tocolysis aims to inhibit uterine contraction long enough for corticosteroid therapy to mature fetal lungs and improve neonatal outcomes. The many different drugs that have been used for the treatment of preterm labour include β2-adrenergic receptor agonists, calcium channel blockers, OXTR antagonists, magnesium sulphate (MgSO4), progesterone, PG synthesis inhibitors, and NO donors. None of these drugs seem to be effective in regularly prolonging pregnancy beyond 48 hours and there seems to be little consensus amongst international tocolytic guidelines as to which are the best tocolytics.[2,7,8]

Most of the current available tocolytic drugs were not specifically developed for tocolysis but for other indications and were found to have tocolytic side effects. Some of these drugs are used off-label as second-line tocolytics.[8]

β2-adrenergic receptor agonists

Drugs that belong to this group are salbutamol, terbutaline, ritodrine, and isoxsuprine.[2,4] They activate adenyl cyclase, thereby increasing cAMP and consequently protein kinase A (PKA). PKA regulates the phosphorylation and therefore inactivation of MLCK.[2]

Salbutamol is usually administered as a continuous intravenous infusion. Due to the wide distribution of β2-adrenergic receptors throughout the body, the side effects are extensive. They include tachycardia, palpitations, chest pain, dyspnoea, pulmonary oedema, hypokalaemia, hyperglycaemia, flushing, sweating, nervousness, tremors, nausea, and vomiting.[2,4]

Calcium channel blockers

Nifedipine blocks voltage-gated calcium channels and thereby prevents the influx of calcium into the myometrial cells. It seems to be more effective when used before 34 weeks of gestation and is usually administered orally. Maternal hypotension is the most common side effect and may be associated with placental hypoperfusion.[2,4]

OXTR antagonists

Atosiban is a competitive inhibitor of the OXTR as well as the vasopressin-1A receptor. Favourable results were initially shown with in vitro testing, but unfortunately, clinical effectiveness has not been demonstrated.[2]

MgSO4

Magnesium causes a dose-dependent reduction in intracellular calcium concentrations and thereby reduces the force of both spontaneous and oxytocin-induced uterine contractions. Magnesium antagonises calcium by reducing L-type calcium channel opening. Magnesium also possibly reduces intracellular calcium release from the SR. Another proposed mechanism is the reduction of PLC and hence IP3. Unfortunately, there is little clinical evidence that MgSO4 successfully prevents preterm labour. However, it may be useful in providing neuroprotection to premature infants.[2] Side effects of MgSO4 include hypotension, flushing, sweating, nausea, vomiting, blurred vision, headaches, palpitations, and decreased reflexes. It also has the potential to prolong the duration of action of neuromuscular blockers.[4]

Progesterone

Progesterone is a steroid hormone that is produced by placental tissue during pregnancy. It is pro-gestational and is thought to maintain uterine quiescence through the expression of genes associated with the contraction mechanisms of myometrial smooth muscle and by inhibiting the production of PGs. Progesterone also inhibits phosphodiesterase-4, which is responsible for cAMP inactivation. Furthermore, progesterone inhibits calcium influx and release from the SR and hyperpolarises cell membranes through the activation of potassium channels. It may also inhibit oxytocin binding.[2,7]

Progesterone can be administered orally, intramuscularly, and vaginally. Some evidence suggests that it sensitises the myometrium to other tocolytics, such as the β2-adrenergic receptor agonists, calcium channel blockers, and PG synthesis inhibitors, and that its main role may be to maintain tocolysis after the successful arrest of labour by other tocolytics.[2,7]

PG synthesis inhibitors

This group of drugs includes COX inhibitors, also known as nonsteroidal anti-inflammatory drugs (NSAIDs). The tocolytic effects of both non-specific COX and COX-2-specific inhibitors have been studied. NSAIDs prevent the breakdown of arachidonic acid into the various PG isoforms.[2]

During labour, the production of PGs and COX-2 increases in the fetal membranes and the myometrium.[9] Inhibition of COX therefore reduces the production of PGs and thereby reduces myometrial contraction.[2,9] Unfortunately clinical trials have not shown a significant reduction in the incidence of preterm labour with either indomethacin or selective COX-2 inhibitors.[2] The COX-2 inhibitors have also been associated with severe fetal and neonatal side effects, such as impaired renal function, oligohydramnios, necrotising enterocolitis, and intraventricular haemorrhage. Gastrointestinal side effects are common in mothers. Due to the risk of premature closure of the ductus arteriosus, NSAIDs should only be administered for short periods before 32 weeks of gestation.[2,4]

NO donors

NO activates guanyl cyclase and therefore increases the production of cGMP and protein kinase G (PKG). PKG inhibits calcium influx. Unfortunately, several randomised controlled trials have shown that nitroglycerin does not delay labour or improve neonatal outcomes.[2] Hypotension, headache, and platelet dysfunction are some of the side effects.[4]

Novel tocolytics

2-aminoethoxydiphenyl borate (2-APB), glycyl-H-1152 dihydrochloride (GH), and HC-067047 are currently being investigated as novel tocolytics. 2-APB is an IP3 receptor inhibitor and blocks various routes of calcium influx into the myometrium. GH is a selective inhibitor of rho-kinase, which plays a role in the phosphorylation of myosin light chains. HC-067047 is an inhibitor of TRPV4, a non-selective cation channel involved in calcium influx.[8]

Volatile anaesthetic agents

Halothane, isoflurane, sevoflurane, and desflurane all decrease myometrial contractility in in vitro studies. The inhibitory potency of halothane, sevoflurane, and desflurane seems to be similar and possibly greater than that of isoflurane. At less than one minimum alveolar concentration, oxytocin can re-establish uterine contractility reduced by the volatile anaesthetic agents.[10]

The underlying mechanism of volatile-induced myometrial relaxation is unclear. Inhibition of various potassium channels and L-type calcium channels as well as changes to myofilament calcium sensitivity have been proposed.[10]

The effects of propofol and dexmedetomidine on the myometrium

In vitro and in vivo animal studies have demonstrated that propofol reduces oxytocin-induced myometrial contraction and dexmedetomidine increases it. The underlying mechanisms are unclear.[11]

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References

1. Gizzo S, Patrelli TS, Gangi SD, et al. Which uterotonic is better to prevent the postpartum hemorrhage? Latest news in terms of clinical efficacy, side effects, and contraindications: a systematic review. Reprod Sci. 2013;20(9):1011-9. https://doi.org/10.1177/1933719112468951.
2. Arrowsmith S, Kendrick A, Wray S. Drugs acting on the pregnant uterus. Obstet Gynaecol Reprod Med. 2010;20(8):241-7. https://doi.org/10.1016/j.ogrm.2010.05.001.
3. Dyer RA, van Dyk D, Dresner A. The use of uterotonic drugs during caesarean section. Int J Obstet Anesth. 2010;19(3):313-9. https://doi.org/10.1016/j.ijoa.2010.04.011.
4. Diedericks BJS, Brandl AB. Smooth muscle agents. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 1st ed. Centurion: MedPharm Publications; 2012. p. 321-7.
5. Fitzgerald PA, Klonoff DC. Endocrine drugs. In: Katzung BG, editor. Basic clinical pharmacology. 7th ed. Connecticut: Appleton & Lange; 1998. p. 603-18.
6. Farina Z, Fawcus S. Oxytocin-ensuring appropriate use and balancing efficacy with safety. S Afr Med J. 2015;105(4):271-4. https://doi.org/10.7196/SAMJ.9179.
7. Navathe R, Berghella V. Progesterone as a tocolytic agent for preterm labor: a systematic review. Curr Opin Obstet Gynecol. 2016;28(6):464-9. https://doi.org/10.1097/GCO.0000000000000327.
8. Hossain MR, Tolosa JM, Young RC, Smith R, Paul JW. Assessing the potency of the novel tocolytics 2-APB, glycyl-H-1152, and HC-067047 in pregnant human myometrium. Reprod Sci. 2023;30(1):203-20. https://doi.org/10.1007/s43032-022-01000-2.
9. Sawdy RJ, Sullivan MHF, Bennett PR. The effects of non-steroidal anti-inflammatory compounds on human myometrial contractility. Eur J Obstet Gynecol Reprod Biol. 2003;109(1):33-40. https://doi.org/10.1016/S0301-2115(02)00481-5.
10. Yoo KY, Lee JC, Yoon MH, et al. The effects of volatile anesthetics on spontaneous contractility of isolated human pregnant uterine muscle: a comparison among sevoflurane, desflurane, isoflurane, and halothane. Anesth Analg. 2006;103(2):443-7. https://doi.org/10.1213/01.ane.0000236785.17606.58.
11. Kimizuka M, Tokinaga Y, Azumaguchi R, et al. Effects of anesthetic agents on contractions of the pregnant rat myometrium in vivo and in vitro. J Anesth. 2021;35(1):68-80. https://doi.org/10.1007/s00540-020-02866-9.

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Placental physiology

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Introduction

The embryo implants into the endometrium (decidua), and it rapidly progresses into a sphere enveloping the amniotic cavity with a local thickening, the placenta.[1] The placenta is a vital organ that gradually forms during the first three months of pregnancy. It is a temporary organ whose genetic characteristics are identical to those of the fetus. The several layers that form this organ (parenchyma, chorion, amnion, and umbilical cord) need to develop normally to allow proper function during pregnancy.

Anatomy and blood flow

The placenta develops from the blastocyst shortly after implantation. Due to hormonal changes in the mother (e.g. increase in luteinising hormone), degrading enzymes released, autocrine growth factors (e.g. human chorionic gonadotropin [hCG]), and insulin growth factor (IGF), the blastocyst further invades the endometrium. Gastrulation (reorganisation into a multilayered and multidimensional structure) now takes place.

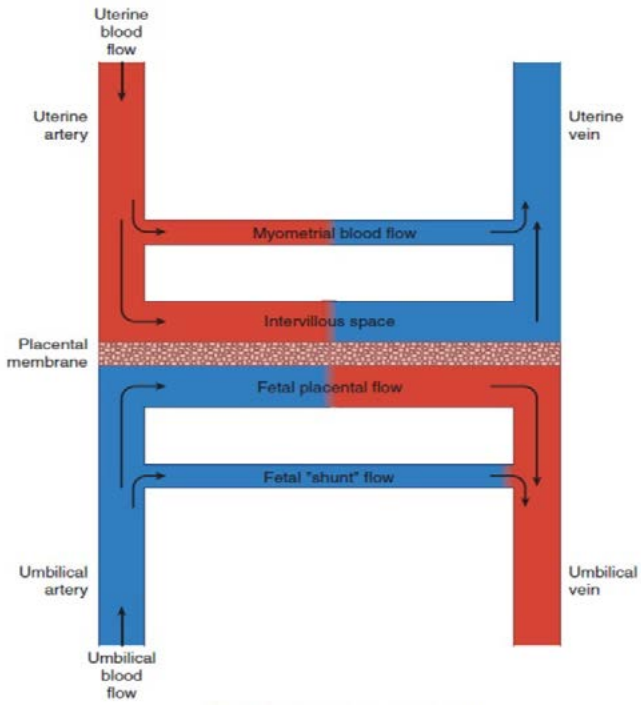

Figure 1: The uteroplacental circulation[4]

At term, the human placenta is a villus haemomonochorial structure, the maternal blood is in direct contact with the fetal villus, which is composed of a single layer of trophoblasts (monochorial).[2] Abnormal proliferation of trophoblasts results in gestational trophoblastic disease.

Within 11 days of fertilisation, the trophoblast forms two layers, the cytotrophoblast and the syncytiotrophoblast (STB), containing lacunar lakes. The lacunae enlarge with the trophoblasts forming villi, which consist of the vascularised core of the cytotrophoblast covered by the STB. The maternal spiral arteries are eroded by the trophoblast, which then flows directly into the intervillous space.

The functional unit of the placenta is known as the uteroplacental unit. This unit contains fetal and maternal components that are arranged in a specific manner to allow maternal and fetal blood to come into close proximity to each other, without mixing. The fetal side of the placenta forms the chorionic plate while the maternal side forms the basal plate. The area between these two plates is known as the intervillous space.[3]

Uterine blood flow (UBF) comes from the uterine arteries with minor contributions from the ovarian arteries. Maternal blood travels through the spiral arteries and reaches the intervillous space where it pools, surrounded by villi that contain fetal capillaries. These capillaries will receive deoxygenated blood from the fetus via two umbilical arteries. Maternal-fetal exchange of nutrients, respiratory gases, fetal waste, and other substances takes place at the terminal villi. Maternal blood then returns to the maternal circulation through the uterine veins, and oxygenated blood travels to the fetus via the umbilical vein (Figure 1).[4]

In a term pregnancy, the uterus receives 500–900 ml/min or 10% of the maternal cardiac output (compared to 50–100 ml/min in the non-pregnant uterus). The majority of this (80–90%) supplies the placenta while the rest goes to the myometrium and non-placental endometrium. To accommodate this increase in blood flow, the spiral arteries of the uterus undergo growth and remodelling. The replacement of the tunica media in these vessels results in optimal vasodilation, resulting in uterine arterial

pressure (UAP) being dependent on maternal blood pressure and cardiac output.

The uterine vasculature still maintains intrinsic responsiveness to α-adrenergic agents and possibly β-adrenergic agents, thus affecting uterine vascular resistance (UVR) so that UBF is determined as follows:[5]

$$\text{Uterine blood flow (UBF)} = \frac{\text{uterine arterial pressure (UAP) - uterine venous pressure UVP}}{\text{uterine vascular resistance (UVR)}}$$

$$\text{Uterine perfusion pressure (UPP)} = \text{UAP - UVP}$$

Subsequently, during pregnancy, three major factors decrease UBF: systemic hypotension, uterine vasoconstriction, and uterine contractions. Hypovolemia, aortocaval compression, and sympathetic blockade caused by neuraxial anaesthesia can cause maternal hypotension. Aortocaval compression, certain drugs (e.g. oxytocin), uterine contractions, or skeletal hypertonia (e.g. seizures, Valsalva) can cause an increase in UVP resulting in a decrease in UBF. UVR can be increased by the stress-induced release of endogenous catecholamine, vasopressin release secondary to hypovolemia, exogenous vasopressors (e.g. phenylephrine, ephedrine, and a high dose of local anaesthetics), and compression of the endometrial spiral arterioles during contractions. Clinical studies have shown phenylephrine and metaraminol are effective in treating pregnant women and are associated with less fetal acidosis compared to ephedrine.[5] Hypertensive disorders are associated with decreased UBF due to generalised vasoconstriction.[4]

Function

The placenta has numerous responsibilities with the terminal villi acting as a functional unit allowing the maternal-fetal exchange of gases and nutrients. Oxygen, water and electrolytes, hormones, and nutrients are provided by maternal blood, while the fetus excretes water, urea, hormones, carbon dioxide, and other waste products. The maternal and fetal blood do not mix, instead, blood flow moderates the passive or active transport of products between the vasculature.[6]

Gas exchange

Fetal respiratory movements can be seen as early as 11 weeks. There is no gaseous exchange, instead oxygenation and elimination of carbon dioxide take place by simple diffusion across the fetal membrane. The oxygen supply to the fetus is at 8 ml/kg/min and is achieved by a cord blood flow of 165–330 ml/min.

The rate of diffusion of a gas is dependent on its lipid solubility and size. Because of the differences in solubility, carbon dioxide diffuses across the lipid membrane 20 times faster than oxygen, and several other factors affect the movement of respiratory gases between maternal and fetal circulation. Critical to this process is the concentration gradient between fetal and maternal blood: structural differences in maternal and fetal haemoglobin and their oxygen dissociation curves, the double Bohr effect, and the double Haldane effect.[2,7,8] The fetus compensates for low PO_2 by having a higher haematocrit (Hb 15–17 g/dl) and a left-shifted oxygen dissociated curve with HbF having a greater affinity for oxygen. Consequently, the average oxygen content of fetal blood is greater than maternal blood.[7]

Metabolic transfer

Nutrients are obtained from maternal blood. Glucose, the principal source of energy for the fetus, is transferred by transporter proteins (seven GLUT isoforms have been identified) through the process of facilitated diffusion and converted into glucose-6-phosphate or glycogen. An increased expression of GLUT-1 has been seen in pregestational diabetes mellitus.[9] Triglycerides and fatty acids are transported directly from the mother in early pregnancy, while other lipids required for growth and development are produced in the fetus. Cholesterol is an important precursor for progesterone and oestrogen. Amino acids, which are higher in fetal blood than in maternal blood, are transferred by active transport involving an enzymatic process (ATPase). Protein synthesis is initially 1 g/day and becomes 7.5 g/day at term.[10]

Water and electrolytes

Various aquaporin isotypes form specific water channels that allow rapid transcellular movement of water in response to osmotic and hydrostatic pressure gradients.[11] This movement will be altered when the mother receives hypo- or hypertonic intravenous fluid.[2,11] Sodium, potassium, and chloride cross the fetal membrane via simple diffusion, while calcium, phosphorus, and iron cross by active transport.[8]

Endocrine

The placenta releases placental growth factor to prepare the maternal body for cardiovascular adaption. This factor also promotes fetal development and maturity. Human chorionic somatomammotropin (HCS), or human placental lactogen (HPL), promotes breast development and changes the maternal metabolism to decrease the woman's insulin sensitivity, thus allowing more glucose to be available for the fetus.[6] In the fetal circulation, HPL modulates embryonic development, regulates intermediary metabolism, and stimulates the production of insulin-like growth factor, insulin and adrenocortical hormones, and pulmonary surfactant.[3]

There is a slow movement of the following hormones across the placenta: insulin, steroids from the adrenals, thyroid, and chorionic gonadotropin/placental lactogen. This results in their concentration being lower than in maternal plasma. Parathormone and calcitonin do not cross the placenta. The placenta also has multiple enzymatic functions including the production of diamine oxidase, which inactivates circulatory pressor amines, oxytocinase, which neutralises oxytocin, and phospholipase A_2, which synthesises arachidonic acid.[12]

Immunological

Antibodies and antigens in immunological quantities can cross the placenta in both directions. The placenta can also metabolise

numerous substances and protect against microbes. Essential role players in the protection of the fetus include macrophages in the stroma of the chorionic villi and STBs. In addition, leucocytes can be found in the decidua of the endometrium.[6]

Anticoagulant

The STB takes on vascular characteristics such as the presence of von Willebrand factor (vWF), CD31 makers, adhesion molecules, and coagulation components. Thrombosis of the placental vasculature would be devastating, subsequently, there needs to be an efficient mechanism for fast activation and localised regulation of coagulation. Procoagulant (e.g. tissue factor and plasminogen activator inhibitors) and anticoagulant (e.g. tissue factor pathway inhibitor, thrombomodulin, nitric oxide, ADPase, carbon monoxide, a membrane glycoprotein that activates protein C, and annexin V) components are present on the placental vascular endothelial cells and STB. Reduced annexin V has been associated with the presence of antiphospholipid antibodies. Activation of coagulation may be a favoured process as seen by the elevation of fibrin deposits in pathological states.[13]

Placental drug transfer

Several factors affect drug transfer across the placenta and can be summarised as physical or pharmacological. Physical factors include placental surface area, placental thickness, pH of maternal and fetal blood, placental metabolism, UBF, and the presence of placental drug transporters. Pharmacological factors are the molecular weight of the drug, lipid solubility, pKa, protein binding, and concentration gradient across the placenta.[8] The mechanisms of drug transfer are discussed below.

Diffusion

Small, nonpolar and uncharged particles can cross the lipid bilayer via simple diffusion (passes directly across the lipid membrane or through channel proteins). Fick's law of diffusion determines this movement and it can be used to calculate the amount of oxygen and carbon dioxide that passes directly through the lipid bilayer.

Net flux (amount transported) = diffusing capacity of membrane (DM) × (P1 - P2)

$$\text{Where diffusing capacity } \alpha = \frac{\text{A (solubility)}}{\text{T } (\sqrt{\text{MW}})}$$

(P1 - P2) is the pressure gradient over a membrane where P1 is maternal and P2 is fetal, A is the surface area of the membrane, T is the thickness of the membrane, and √MW is the square root of the molecular weight of the particle.

Therefore, charged or large molecules will have a slower passage through the membrane. Carrier proteins in the lipid bilayer increase the rate of diffusion by creating channels for these particles to travel (facilitated diffusion). Hormones will regulate whether the channels are open or closed. Glucose is transported by facilitated diffusion.[14]

Osmotic and hydrostatic pressure (bulk flow)

Water is a polarised molecule and its passage is driven by osmosis and hydrostatic pressure, it is carried by aquaporins in the placental membrane.[11] This bulk flow drags along dissolved solutes.

Active transport

Active transport is similar to facilitated diffusion, except that cellular energy is used to move the molecules against the concentration gradient. When ATP is hydrolysed for energy, this is called direct active transport (e.g. Na/K ATPase pump, amino acids, calcium, and phosphate).[2]

Vesicular transport

Large macromolecules cross from maternal to fetal circulation through pinocytosis, which is a form of energy-requiring vesicular transport. The cell membrane forms a vesicle by surrounding the macromolecule. This vesicle then fuses with another cellular membrane releasing the macromolecule. Immunoglobulins and iron are examples of products transferred through this process.[5]

Breaks

The placenta is not an impenetrable structure and occasionally fetal and maternal blood may mix. This Rh sensitisation occurs usually at delivery.[5]

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References

1. Ebbesen P. Placenta physiology. In: Ambroise-Thomas P, Petersen E, editors. Congenital toxoplasmosis. Paris: Springer; 2000. https://doi.org/10.1007/978-2-8178-0847-5_3.
2. McNanley T, Woods J. Placental physiology. Glob libr women's med; 2008. https://doi.org/10.3843/GLOWM.10195.
3. Nel D. Placental physiology. FCA part 1 anaesthetic refresher course; 2016.
4. Frölich MA. Maternal & fetal physiology & anesthesia. In: Butterworth IV JF, Mackey DC, Wasnick JD, editors. Morgan & Mikhail's clinical anesthesiology. 6th ed. New York: McGraw-Hill Education; 2018.
5. Hopkins AN, Berger JS. Placental physiology. In: Freeman BS, Berger JS, editors. Anesthesiology core review: part two advanced exam. New York: McGraw-Hill Education; 2016.
6. Kapila V, Chaudhry K. Physiology, placenta. Treasure Island: StatPearls Publishing; 2023.
7. Vaupel P, Multhoff G, editors. Blood flow and respiratory gas exchange in the human placenta at term: a data update. Adv Exp Med Biol. 2022;1395:379-84. https://doi.org/10.1007/978-3-031-14190-4_62.
8. Griffiths SK, Campbell JP. Placental structure, function and drug transfer. BJA Education. 2015;15(2):84-9. https://doi.org/10.1093/bjaceaccp/mku013.
9. Illsley NP, Baumann MU. Human placental glucose transport in fetoplacental growth and metabolism. Biochim Biophys Acta Mol Basis Dis. 2020;1866(2):165359. https://doi.org/10.1016/j.bbadis.2018.12.010.
10. Allen P, Zafar F, Mi J, et al. Risk stratification for congenital heart surgery for ICD-10 administrative data (RACHS-2). J Am Coll Cardiol. 2022;79(5):465-78. https://doi.org/10.1016/j.jacc.2021.11.036.
11. Sha X-y, Xiong Z-f, Liu H-s, Di X-d, Ma T-h. Maternal-fetal fluid balance and aquaporins: from molecule to physiology. Acta Pharmacol Sin. 2011;32(6):716-20. https://doi.org/10.1038/aps.2011.59.
12. Asif. Function of placenta [Internet]. Rnnursingexam; 2021 [updated 2023]. Available from: https://rnnursingexam.com/2021/04/function-of-placenta.html. Accessed 19 August 2023.
13. Lanir N, Aharon A, Brenner B. Procoagulant and anticoagulant mechanisms in human placenta. Semin Thromb Hemost. 2003;29(2):175-84. https://doi.org/10.1055/s-2003-38833.
14. Burton GJ, Sibley CP, Jauniaux ERM. Placental anatomy and physiology. 8th ed. Elsevier Inc.; 2021.

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Pain physiology and pain pathways

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The presence of pain is a protective mechanism that serves to prevent the body from further harm. However, when pain becomes pathological, it becomes a socio-economic disease burden that impacts a significant portion of the population.

This article aims to discuss the physiology of pain that forms the basis for understanding the processes that allow pain to become chronic. It describes the definition of pain and the various types of pain receptors involved in the processing and perception of pain. The physiology, pathways and processes involved in the activation and ongoing experience of pain are well described in terms of four distinct events, known as transduction, transmission, modulation, and perception.

The events described lend emphasis to the subjectivity of pain and the importance of a multidisciplinary approach to the effective management of chronic pain conditions.

Keywords: pain physiology, pain pathways

Introduction

The presence of pain serves as a physiologically protective mechanism by minimising movement, thus promoting healing and inducing a withdrawal reflex that protects from further harm.[1] Pain becomes pathological or chronic when it extends over a long period, usually defined as three months, or represents low levels of pathology that do not explain the presence or severity of pain.[1,2] The result is a disease burden reported to affect one out of five South Africans and 20% of the population worldwide.[1] Therefore, a thorough understanding of pain physiology is crucial in the diagnosis and effective management of chronic pain conditions.

What is pain?

The phenomenon of pain was first described in 1979 by the International Association for the Study of Pain (IASP), updated in 2020, and is now defined as an unpleasant sensory and emotional experience associated with or resembling – as opposed to being described as such – actual or potential tissue damage.[3,4] The new definition emphasises that the inability to verbally communicate or express pain does not invalidate the experience thereof.[2,3] Pain is not specific to age, sex, or species, and is a subjective experience influenced by physical, psychological, social, spiritual, and environmental factors.[1] Consequently, a multidisciplinary approach to pain management is a critical and non-negotiable necessity.

Pain receptors

Nociceptors are present as free nerve endings of nerve fibres in skin, muscles, joints, and viscera.[2] There are three types of nociceptors:

- High-threshold mechanoreceptors respond to pinch and pinprick.[4]
- Silent nociceptors are activated when sensitised by inflammatory mediators.[4]
- Polymodal nociceptors respond to extreme temperatures, excessive pressure, and noxious chemical substances, such as hydrogen ions, potassium, adenosine triphosphate, bradykinin, serotonin, cytokines, and histamines.[4–6] They are further sensitised to low-intensity stimuli by prostaglandins, leukotrienes, and the excitatory neurotransmitters calcitonin gene-related peptide (CGRP), substance P, and glutamate.[4–6] Protons and serotonin act directly on ion channels on the cell membrane, but other sensitisers may bind to membrane receptors and activate second-messenger systems via G-proteins.[4]

Patterns of gene expression and the presence or absence of certain markers have been used to identify or define subtypes of nociceptors.[4] Voltage-gated sodium channels (VGSC) Nav 1.7, tetrodotoxin-resistant Nav 1.8, and Nav 1.9 are expressed exclusively in the cell bodies of nociceptors. The Piezo-type mechanosensitive ion channel component (PIEZO2) and the transient receptor potential vanilloid receptor (TRPV1) are examples of such markers.[4,7] TRPV1 and PIEZO2 are thermal and mechanically sensitive ion channels that have a role in allodynia, which is defined as pain due to a stimulus that does not normally provoke pain.[4] TRPV1 is activated by capsaicin, hydrogen ions, and heat.[2,4,6] PIEZO2, on the other hand, is the major mechanical sensor in nerves required for the perception of touch.[4,7]

Pain processing and pathways

The processes involved in the activation and ongoing experience of pain are better understood when described in terms of four distinct events that allow the nociceptor to convey noxious information from peripheral tissues to the central nervous system.[2] These events are known as transduction, transmission or conduction, modulation, and perception.[5]

Transduction

Transduction is the process of converting the "energy" from a noxious stimulus into an electric signal or action potential, which is then transmitted along first-, second- and third-order neurons.[1,2,5,6] The generator potentials responsible for the production of an action potential are the resting and threshold potentials of a neuron, which are approximately -70 and -55 mV, respectively.[2,9] When threshold potential is achieved, the sodium voltage-gated channels present on first-order neurons open, which act as molecular transducers, resulting in the influx of sodium and the depolarisation of the neuron.[1,2,8,9] Once the peak potential of +30–40 mV is achieved, potassium channels open allowing the efflux of potassium, leading to the repolarisation of the neuron.[8,9]

First-order neurons have a single bifurcated axon, sending one end to peripheral tissues and the other end to the dorsal horn of the spinal cord grey matter where they synapse with second-order neurons.[6] They are the site of energy transduction and have cell bodies that lie within the dorsal root or trigeminal ganglia and serve as the supply depot for the neuron, supplying the nerve with the proteins, lipids, and neurotransmitters needed for action potential propagation and pain transmission.[2] In the presence of nerve injury, an increase in the production of transducer proteins, sodium channels, and inflammatory receptors and proteins occurs within the cell body, making the nociceptive more responsive to stimuli.[2,4,5]

Two main types of first-order neuronal sensory fibres respond to noxious stimuli. Firstly, slow-conducting unmyelinated C-fibres transmit dull and diffuse pain. Secondly, fast-conducting thinly myelinated A-delta fibres transmit sharp and well-localised pain.[4,6-9] Thickly myelinated A-beta fibres were thought to respond mainly to non-painful stimuli, such as vibration and light touch.[4,7] However, there is emerging evidence of their role in ultrafast nociception.[4,7]

Transmission

When the action potential generated by the first-order neuron reaches the axon terminal, calcium enters the presynaptic terminal through calcium voltage-gated channels leading to the release of glutamate, which then crosses the synaptic cleft to activate the postsynaptic AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor.[1,9] This leads to the transmission and propagation of the noxious signal to ascending tracts, such as the spinothalamic and spinoreticular tracts, which then relay the signal to third-order neurons.[1,4,6] Whilst the action potential threshold is regulated by potassium and calcium voltage channels, sodium voltage-gated channels Nav 1.7, Nav 1.8, and Nav 1.9 determine the threshold for initiation.[2,9] The channel responsible for signal propagation, however, is Nav 1.6.[2,9]

In the dorsal horn, first-order neurons synapse with second-order neurons, which in turn synapse in thalamic nuclei with third-order neurons.[6] As the fibres of first-order neurons enter the spinal cord, they segregate according to size, with small unmyelinated fibres becoming medial, and larger myelinated fibres becoming lateral.[6] Although most enter the dorsal horn in the ventrolateral bundle of the dorsal (sensory) root, 30% of C-fibres enter via the ventral (motor) root.[4,6] For this reason some patients will continue to feel pain even after transection of the spinal root.[6] A-beta fibres enter medial to the dorsal horn and pass without synapse to the dorsal columns.[4] Upon entry, the nerve roots may ascend or descend one or two segments higher or lower than the segment of origin before synapsing with second-order neurons.[6] Some communicate with second-order neurons through interneurons.[6]

The dorsal horn is divided into six Rexed laminae.[4,6] A-delta fibres terminate in laminae I and V and are the important areas for the modulation and localisation of pain.[4] Laminae I and V also represent the points of convergence between somatic and visceral afferent fibres, which are represented clinically by referred pain.[6]

A-beta and C-fibres that terminate in lamina II, also known as the substantia gelatinosa, send collateral branches to the dorsal horn which terminate in several laminae.[4,6] A-beta fibres also synapse directly with terminals of C-fibres in lamina II.[4]

There are three types of second-order neurons:

- Nociceptive specific neurons are found in laminae II and III and respond to high-threshold noxious stimuli.[4,6]
- Wide dynamic range (WDR) neurons are found in laminae V and VI and respond to a range of sensory stimuli.[4,6]
- Low-threshold neurons respond to innocuous stimuli.[4]

Whilst the axons of some second-order neurons may ascend to higher centres ipsilaterally, most located in laminae I and V decussate close to their dermatomal level of origin to the contralateral side of the spinal cord before forming the spinothalamic tract. The tract lies anterolaterally in the white matter of the spinal cord and divides into the lateral and medial tracts.[1,4,6]

The lateral (neospinothalamic) tract fibres contain axons of second order neurones located in laminae I and V which contribute to thermal and pain sensations.[4] The fibres project to the ventral posterolateral nucleus and carry discriminative aspects of pain such as location, duration, and intensity.[4,6] This is achieved through lateral thalamic third-order neurons that project to the primary and secondary somatosensory cortices in the postcentral gyrus and Sylvian fissure of the cerebral cortex respectively.[1,4,6]

The axons of the medial (paleospinothalamic) tract fibres are located in lamina I and project to the medial thalamus.[4,6] Projections from the spinoparabrachial tract are also responsible for mediating the autonomic and emotional aspects of pain via medial thalamic third-order neurons that project to the insula, hippocampus, amygdala, anterior cingulate gyrus, and prefrontal cortex.[1] Other ascending tracts include the spinoreticular tract, which is thought to mediate the arousal and autonomic responses to pain, the spinomesencephalic tract that projects neurons to the periaqueductal grey (PAG) where descending inhibitory pathways are located, the spinohypothalamic and spinohypothalamic tracts that activate the hypothalamus and evoke emotional behaviour, and the spinocervical tract that ascends uncrossed to the lateral cervical nucleus.[1,6] Some fibres in the dorsal columns that carry light touch and proprioception can respond to pain.[6] These fibres ascend medially and ipsilaterally.[6]

Modulation

The dorsal horn is where modulatory interactions between excitatory and inhibitory interneurons and descending inhibitory tracts from higher centres occur.[4,6] Modulation of pain signals can occur peripherally or centrally and can facilitate or inhibit pain.[1,6]

i. Peripheral modulation

Sensitisation of the nociceptor results in a decrease in the firing threshold, an increase in the frequency discharge to the same stimulus intensity, a decrease in response latency, and spontaneous firing even after the stimulus is no longer present.[4,6] This results in primary hyperalgesia defined as an increased pain response to a painful stimulus.[3]

Secondary hyperalgesia is characterised by red flushing around the site of injury and local tissue oedema and occurs due to the release of substance P and CGRP.[6,9] Substance P degranulates histamine from mast cells, and serotonin from platelets, and is also a potent vasodilator and chemoattractant for leukocytes.[6,9]

ii. Central modulation

Three mechanisms are responsible for central sensitisation at the level of the spinal cord:

- Wind-up or temporal summation and sensitisation of second-order WDR neurons.[6,9] With sustained transduction, substance P and neurokinins A and B are released from the presynaptic terminal.[1,9] These produce a longer-lasting depolarisation of the postsynaptic membrane, resulting in the summation of postsynaptic depolarisations.[6,9] Once the membrane is sufficiently depolarised, the physiological magnesium block of the postsynaptic NMDA (N-methyl-D-aspartate) receptor is removed.[9] Glutamate then binds to the receptor, allowing the ion channel to open and produce a large calcium influx.[9] Activation of the NMDA receptor results in the formation of nitric oxide, which facilitates the release of excitatory amino acids in the spinal cord.[6]
- Receptor field expansion is achieved by the recruitment of dorsal horn neurons of adjacent neurons that become responsive to noxious and non-noxious stimuli to which they were previously unresponsive.[6]
- Enhancement of flexion reflexes observed both ipsilaterally and contralaterally.[6]

Pain suppression is dependent on supraspinal inhibition from higher centres, activity in A-beta collaterals and segmental (spinal) inhibition by endogenous opioids, cannabinoid systems, and inhibitory amino acids such as gamma-aminobutyric acid (GABA) and glycine.[4,6]

In 1965, Melzack and Wall proposed that lamina II inhibitory interneurons can be activated directly or indirectly (via excitatory interneurons) by stimulation of non-noxious A-beta afferents from the skin, which would then suppress transmission in C- fibre afferents and therefore block the pain.[1,4,6] This gateway theory is the working mechanism behind rubbing a painful area and the use of transcutaneous electrical nerve stimulation (TENS) in pain management.[4]

The descending tracts located in the PAG and nucleus raphe magnus (NRM) play a role in the descending inhibition of pain.[1,4,6,9] The PAG receives inputs from the thalamus, hypothalamus, and cortex, as well as collaterals from the spinothalamic tract.[4,6,9] PAG neurons excite cells in the NRM that in turn project to the dorsal horn neurons to block pain signals.[4,6] The NRM is a descending system of serotonin-containing neurons, the stimulation of which results in the release of serotonin, providing profound analgesia.[4] The cell bodies of these neurons are located in the raphe nuclei of the medulla and the axons synapse to cells in laminae II and III.[4] Inhibitory adrenergic pathways originate primarily from the PAG and reticular formation and mediate their anti-nociceptive effect through activation of presynaptic and postsynaptic alpha-2 adrenergic receptors via noradrenaline.[4,6]

The serotonergic and endogenous opiate system that acts via methionine, enkephalin, leucine enkephalin, and β-endorphin is primarily mediated by the NRM and reticular formation.[6] These opioids act presynaptically to hyperpolarise first-order neurons and inhibit the release of substance P.[6] Exogenous opioids act primarily on postsynaptic second-order neurons or interneurons in lamina II.[6]

Perception

The thalamus is the key area for processing information from third-order neurons that project to the cerebral cortex.[1,4,6] The cortical areas involved in this process are referred to as the neuromatrix and comprise the anterior cingulate cortex, insular cortex, primary and secondary somatosensory cortices, and the prefrontal cortex.[1]

The combined process input from third-order neurons evokes pain cognition, perception, and the behavioural response to pain.[1,4,6] Noxious signal interpretation is thus subjective and dependent on expectations and past experiences, as well as biological and environmental factors.[1] These factors collectively lead to behavioural and psychological responses best addressed

by a multidisciplinary team when managing chronic pain conditions.[1]

Conclusion

The events involved in pain conduction from the peripheral nervous system to the central nervous system form the foundational aspects of pain physiology and help to further understand the complex processes that result in chronic pain.

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References

1. Isa AS, Chetty S. Physiology and pathophysiology of chronic pain (part I). South Afr J Anaesth Analg. 2021;27(6):266-70. https://doi.org/10.36303/SAJAA.2021.27.6.2491.
2. Ballantyne JC, Fishman SM, Rathmell JP. Bonica's management of pain. 5th ed. Lippiott Williams & Wilkins; 2018. p. 11-12, 24-34.
3. IASP-PAIN. IASP: terminology. Available from: https://www.iasp-pain.org/resources/terminology/. Accessed 3 August 2023.
4. Steeds CE. The anatomy and physiology of pain. Surgery. 2009;27(12):507-11. https://doi.org/10.1016/j.mpsur.2009.10.013.
5. Isa AS, Chetty S. Physiology and pathophysiology of chronic pain (part II). South Afr J Anaesth Analg. 2022;28(1):11-4. https://doi.org/10.36303/SAJAA.2022.28.1.2497.0
6. Vrooman BM, Youngren KM. Chronic pain management. In: Butterworth IV JF, Mackey DC, Wasnick JD, editors. Morgan and Mikhail's clinical anesthesiology. 7th ed. McGraw Hill; 2022. p. 1071-82.
7. Nagi SS, Marshall AG, Makdani A, et al. An ultrafast system for signalling mechanical pain in human skin. Sci Adv. 2019;5(7):1-10. https://doi.org/10.1126/sciadv.aaw1297.
8. Excitable tissue: nerve. In: Barrett KE, Barman SM, Boitano S, Brooks HL, editors. Ganong's review of medical physiology. 24th ed. New York: McGraw-Hill Medical; 2012. p. 88-92.
9. Yam MF, Loh YC, Tan CS, et al. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8):1-23. https://doi.org/10.3390/ijms19082164.

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Regression analysis basics: making the right choice of type of regression analysis to model clinical data

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Data-driven clinical practice and evidence-based medicine present themselves as critical tenets of medical practice the world over. The use of data to achieve these tenets often involves using known clinical patient presentations and biological data to predict disease outcomes and other post-care events (i.e. major adverse effects of treatment or mortality). These predictions are achieved using statistical techniques, such as hypothesis testing and forecasting or prediction analysis, also accepted as regression analysis.

In its simplicity, regression analysis represents the statistical technique of applying certain mathematical computational equations to determine the relationship between variables. Therefore, in the use of such mathematical equations, a change in a unit of one variable (the independent variable) can lead to a predictable corresponding change in the dependent variable. This corresponding change can be a unit change, in the independent variable, or it can be a quantifiable factor of the unit of change observed in the independent variable.

The current paper takes an introductory and non-technical approach to discuss processes involved in regression analysis. The focus is the understanding and application of linear and logistic regression to clinical data. Other types of regression methods such as lasso, ridge, and polynomial regression analysis are mentioned but not fully discussed.

Keywords: linear regression, logistic regression, prediction, relationship between variables

Introduction

In statistical analysis, regression analysis is a technique used to test the relationships between variables and make predictions based on those relationships.[1] Regression analysis allows researchers and analysts to understand how changes in one variable (often called an independent variable) are associated with changes in another (called a dependent variable).[2] The ability to use the relationship between a dependent variable and an independent variable allows for the prediction of future values of the dependent variable.

This relationship might be causal in nature or deemed to just predict an association. The relationships are explained through variances, simple and multiple correlations, and regression coefficients, in an iterative process of fitting the regression of one variable on others.[1] The current paper serves to introduce the reader to the two most common linear regression models: linear regression analysis and logistic regression analysis.

Linear regression

There are various types of regression analysis methods, which include but are not limited to linear regression, polynomial regression, logistic regression, lasso and ridge regressions.[3] Figure 1 is a representation of the common types of regression analysis methods.

It is important to note that Figure 1 represents linear models in general and not specifically linear regression analysis. Linear regression analysis is one type or form of a linear model, and so are the other regression types in Figure 1.

Linear regression can be termed simple or multiple linear regression. Simple linear regression tests the effect or influence of one variable (independent variable) on a single dependent variable.[2,4] Equation 1 is a mathematical representation of the simple linear regression analysis. This is a general equation for a straight line. The equation is a derivative of a pair of simultaneous equations called normal equations, and the method of using these normal equations to derive a straight-line equation is called the least squares method.[5]

The normal equations are useful for a simple straight-line equation, while linear relations with curving lines require different sets of derivatives.[5] As in the name, multiple linear regression has multiple explanatory or predictor variables, often called independent variables, used to estimate the future value of a dependent variable.[2,4] Equation 2 represents multiple linear regression analysis. Figure 2 describes the statistical assumptions that must be met for linear regression analysis to be performed.

$$y = \beta_0 + \beta_1 x + \varepsilon$$ **Equation 1**[2]

Where **y** is the dependent variable that is made of continuous data points; β_1 is the slope of the line; **x** is the independent

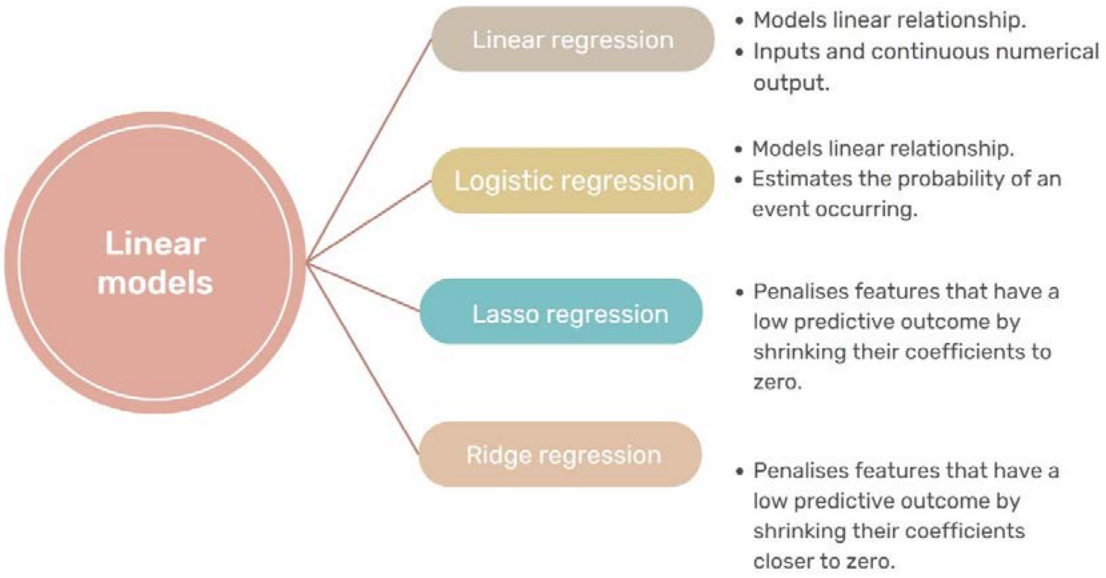

Figure 1: Types of regression models or algorithms (in this case all models assume linearity between inputs and output)

variable; and β_0 represents the intercept or the point where the straight line cuts the y-axis. Ɛ is the error term.

$$y = \beta_0 + \beta_1 x + \beta_2 x + \ldots\ldots \beta_n x_n + Ɛ \qquad \textbf{Equation 2}^2$$

Where x_1, x_2 **and** x_n represent the multiple independent variables. The rest of the equation has the same parameters as the simple linear regression equation (Equation 1).

When plotting a regression model, and fitting the best line, some points will fall on the line and others above or below the line of best fit. Those points vertically above or below the line of best fit are called residuals. The error terms in both equations 1 and 2 relate to these data points that do not perfectly fall on the line of best fit.

When applied in linear regression analysis, the least squares method aims to produce a fit where the sum of all the residuals approximates zero, or the sum is the least or smallest.[3] Therefore, this computation will produce two outcomes, where a) the squared sum of the residuals (SSRes) represents deviation that the model failed to explain or estimate, hence the relationship to the error term, and b) the regression sum of squares (RegSS), which represent the variation in the dependent variable (y) that is explained by the line of best fit.[4]

In the model, the RegSS would be derived as a sum of the squares of vertical distances from the line of best fit to the horizontal line where y is equal to the mean or average. Both the RegSS and the residual sum of squares (RSS) represent deviations from the line of best fit. The former deviation is called explained deviation, while the latter is called unexplained. Figure 3 demonstrates the relationship of the measures of variation in linear regression analysis.

The mathematical relationship of the measures of variation represented in Figure 3 can be described by Equation 3.

Total sum of squares (TSS) = RegSS + ResSS **Equation 3**

Where RegSS is the regression sum of squares (derived from the sum of the square vertical distances between the line of best fit and y is equal to the mean, and ResSS is the residual sum of squares (representing the sum of squared distances of all the vertical points above and below the line of best fit).[4]

Then, to understand how well the regression model is performing, a ratio of the RegSS over the TSS would indicate model performance. As with all ratios, this ratio falls between 0 and 1, with 1 indicating a good and ideal model performance and 0 indicating a poor model. The outcome of this ratio represents a regression correlation coefficient, called the coefficient of

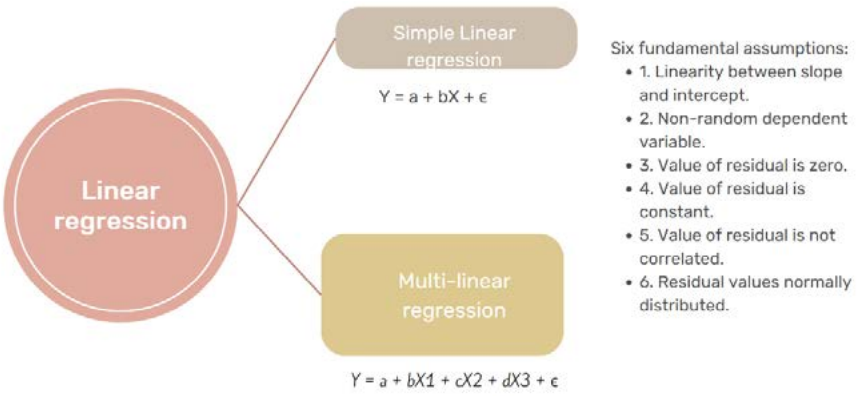

Figure 2: Types of linear regression analysis: simple versus multiple

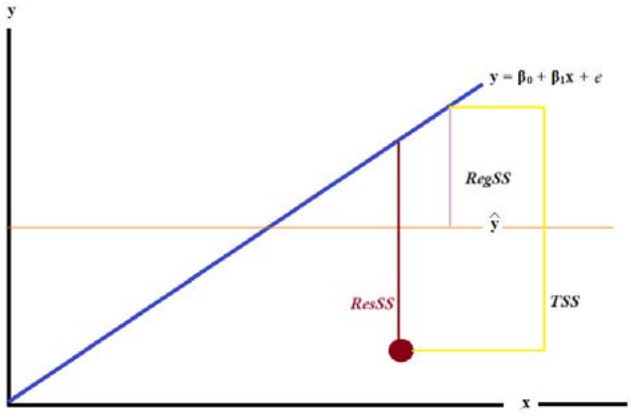

Figure 3: Measures of variation in linear regression analysis

determination (CD), denoted by R^2. It is a measure of correlation because, in classical linear regression analysis, the square root of the CD gives an output mathematically equal to the Pearson correlation coefficient.

To illustrate the simple linear regression, computer-generated dummy data with patient ages and STAT 2020 mortality scores were used. The mortality score was developed in 2009 and updated in 2020. It is a risk stratification tool used to stratify congenital heart disease surgical intervention into groups of increasing risk of mortality.[6] These variables were generated at random and represent no actual patients. To illustrate the concept of simple linear regression, a mortality score is regressed on age, which means age as the independent variable is used to predict the value of a mortality score.

In Figure 4, the *p*-value of the model is significant, indicating that the model is significant as a whole and can be used to describe the linear relationship between age and risk of mortality. Age is statistically significant and has a negative coefficient. This negative statistically significant relationship indicates that as age (in months) increases for paediatric patients with congenital heart defects, which require surgical intervention, the risk score decreases. Older paediatric patients are at a reduced risk of mortality compared to younger paediatric patients, who would in this example have a characteristically high risk score.

In this model, Model SS represents RegSS, which are the deviations explained by the model. The Residual SS represents the error term or the sum of squares of the residuals. Although the model is significant, the R^2 of the model is 6%. As discussed earlier, this comes from the ratio ResSS / TSS. The smaller the ratio, the weaker the model and the closer the ratio is to 1 or 100%, the better the model is at representing the variation in y, which is explained by the model.

The equation of the line is therefore:

STAT 2020 mortality score = 0.45 + (-0.02) * age (in months)

Therefore, when age increases by a unit (one month increase in age), the risk score decreases by 0.02. As such, this model allows us to predict what the risk score can be at any known value of age. At 12 months of age, the risk score can be calculated to be 0.21 = 0.45 + (-0.02 * 12).

Once a model such as in Figure 4 has been developed, the quality of the model must be tested. Several post-model tests, based on the assumptions that were made before the modelling process, are used to assess whether the developed model is reliable. The most used tests for the quality of the model include:

a. The y-estimates must fall within the range of the sample y-values. If this condition is not satisfied, it may be possible that at extreme ends, the relationship of y to x is non-linear.
b. The second condition to test is the distribution of the residuals. In a normal distribution, the data are symmetrical around the mean, and when testing the distribution of the residuals, it would be expected for the polygon to peak around zero.[7]
c. Test the variation of the residuals. A test of homoscedasticity or heteroscedasticity is often performed, where the variance of the residuals across a range of x-values is tested. An even variance, called homoscedasticity, is a desired outcome. There are statistical tests such as the Breusch-Pagan test or the White test for this equality of variance.
d. The independence of residuals otherwise represented as autocorrelation should be tested. It is desired that the residuals must be independent and not autocorrelated. A Breusch-

```
. regress STAT2020_score Age
```

Source	SS	df	MS		
				Number of obs	= 243
				F(1, 241)	= 14.82
Model	1.55362034	1	1.55362034	Prob > F	= 0.0002
Residual	25.2654743	241	.104835993	R-squared	= 0.0579
				Adj R-squared	= 0.0540
Total	26.8190947	242	.110822705	Root MSE	= .32378

STAT2020_s~e	Coefficient	Std. err.	t	P>|t|	[95% conf.	interval]
Age	-.0194887	.0050625	-3.85	0.000	-.0294611	-.0095163
_cons	.4452594	.0267026	16.67	0.000	.392659	.4978598

Figure 4: STAT output for linear regression analysis where age is used to predict the risk of mortality score

Godfrey LM test may be computed to test the null hypothesis on the independence of the residuals.

e. Finally, a test for missing variables may be performed to assess the quality of a simple linear regression model.[2] A Ramsey RESET test can be performed and it will indicate if the model performs better if additional variables are added.

Figures 5, 6, and 7 represent the STATA outputs for the tests in b to e.

```
. predict residuals, resid
(6 missing values generated)

. swilk resid

                    Shapiro-Wilk W test for normal data

    Variable |   Obs        W         V         z       Prob>z
-------------+-------------------------------------------------
   residuals |   243    0.79745   35.829     8.315    0.00000
```

Figure 5: STATA output showing the generation of residuals as a new variable, then testing distribution

In Figure 5, the residuals are first generated as a variable in the data set. Then a Shapiro-Wilk test is applied to ascertain the nature of the probability of distribution of the residuals. The high significant *p*-value indicates that the residuals are not normally distributed. Figure 6 presents the two possible tests for testing the equality of variance of the residuals.

A Breusch-Godfrey test for autocorrelation tests the null hypothesis that postulates no autocorrelation and if significant, the null would be rejected. Finally, Figure 7 represents the result of the Ramsey RESET test.

After developing the model and testing the quality of the model, it can be accepted that although the model has a significant F statistic, and the relationship of age to the mortality risk score was found to be significant, a better model may be possible when other variables are added to the model to enhance the understanding of factors related to mortality in this case.

Although linear regression analysis has numerous applications in medical research, it is often limited by the nature of the outcome variable being studied.[2] It is limited to studying outcomes that are continuous, such as changes in blood pressure. However, the presence or absence of a specific outcome of medical intervention and factors associated with such outcomes are often the desired knowledge. These intervention outcomes can be adverse effects of a new treatment regime compared to a standard of care, or in-hospital mortality, and have binary dependent variables that cannot be studied using linear regression analysis. For binary outcomes, logistic regression analysis is the correct type of regression to test the linear relationship between inputs and output.[2,3]

Logistic regression

Unlike in linear regression analysis, the estimating equation or method in logistic regression is the maximum likelihood (ML) method. The ML method uses a likelihood function, which is a probability function, where the probability of a certain binary outcome (Y) is the highest. This method allows for determining how the probability of success [P(Y) = 1)] can be affected by the presence of predictor variables (predictor variables that also have a probability of occurring in the population being studied).

In the previous linear regression model, the effect of age on the mortality risk score was tested. In a logistic regression, where the dependent variable can be mortality (where 1 means mortality present and 0 indicates the absence, with either state having an

```
. hettest, rhs

Breusch-Pagan/Cook-Weisberg test for heteroskedasticity
Assumption: Normal error terms
Variable: All independent variables

H0: Constant variance

    chi2(1) =  10.87
Prob > chi2 = 0.0010
```

```
. imtest, white
White's test
H0: Homoskedasticity
Ha: Unrestricted heteroskedasticity

    chi2(2) =  11.12
Prob > chi2 = 0.0038

Cameron & Trivedi's decomposition of IM-test

---------------------------------------------------
              Source |       chi2     df       p
---------------------+-----------------------------
  Heteroskedasticity |      11.12      2   0.0038
            Skewness |      12.39      1   0.0004
            Kurtosis |       1.83      1   0.1758
---------------------+-----------------------------
               Total |      25.35      4   0.0000
---------------------------------------------------
```

Figure 6: Test for equality of variance of the residuals

```
. estat ovtest

Ramsey RESET test for omitted variables
Omitted: Powers of fitted values of STAT2020_score

H0: Model has no omitted variables

F(3, 238) =   7.13
 Prob > F = 0.0001
```

Figure 7: Ramsey RESET test with a significant *p*-value, indicating that the model misses some additional predictors

associated probability), it may be important to establish how the probability of mortality can be affected by the presence of comorbid disease in a patient. In this case, it may be possible that the presence of the comorbid disease may increase the probability of mortality. This conjecture is based on the premise that for non-mutually exclusive events (the presence of comorbid disease can occur together with mortality, and each event has a probability), probabilities are multiplicative and not additive.[8]

The logistic regression model also applies a mathematical formula in testing the relationship of the binary outcome, with independent variables that can also be binary or categorical. When the coefficients are exponentiated, the relationship of how one status affects the probability of the other status can then be presented as the odds of the latter occurring.[9] It is similar to linear regression but differs in the outcome variable (binary outcome) and has similar assumptions. Since it models the probability of an outcome that has a chance of being in one state or the other (outcome present versus outcome absent), this ratio is modelled as a logarithm of the chance of that outcome, hence the need to exponentiate the coefficient to attain interpretable odds ratios.[10] Pandis describes the mathematical equation to model this outcome and is called a logit.[9] Equation 4 represents the mathematical equation of the logistic regression. The deferential steps to derive the equation can be found in Pandis, 2017.[9]

$$\text{Log}(p/1 - p) = \beta_0 + \beta_1 x_1 + \beta_2 X_2 + \ldots \beta_n X_n$$

When developing logistic regression analysis, the analyst can either start from a full model and progress to remove very insignificant variables, one variable at a time (a process called stepwise backward regression analysis); or the starting point can be a null model, with only the intercept, and progress forward to add predictors.[10] To illustrate a logistic regression and interpret the results, the same data that were used for the linear regression analysis were used here.

Additionally, the computer-generated data included data on morbidity and mortality. As in linear regression analysis, once the logistic regression model is built, the next step is to assess the quality of the model, and similarly, there are a set of tests that can be performed.

An important consideration when setting off to compute a logistic regression analysis is the sample size. Smaller sample sizes with multiple variables produce bad-quality logistic regression models (models that have a high chance of overestimating the effect measured).[11] An events per variable (EPV) approach is a popular method used to avoid the overestimating problem due to insufficient sample size.[11] EPV is derived using the number of observations in the smaller of the two outcome groups, in relation to the number of predictor variables identified to be used in the model.[11,12] These variables are called candidate predictors because it may compromise the model to use all of them in a saturated model. A rule of thumb often cited when using the EPV is that an EPV of 10 is acceptable.[12]

```
. logit  Mortality  Morbidity STAT2020_score Age

Iteration 0:   log likelihood = -47.745809
Iteration 1:   log likelihood = -46.081753
Iteration 2:   log likelihood =  -44.20935
Iteration 3:   log likelihood = -44.196562
Iteration 4:   log likelihood = -44.196531
Iteration 5:   log likelihood = -44.196531

Logistic regression                               Number of obs =     242
                                                  LR chi2(3)    =    7.10
                                                  Prob > chi2   =  0.0688
Log likelihood = -44.196531                       Pseudo R2     =  0.0743

------------------------------------------------------------------------------
   Mortality | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
   Morbidity |    1.02557   .8520574     1.20   0.229    -.6444321    2.695571
STAT2020_sc~e|   1.210641   .7198585     1.68   0.093    -.2002554    2.621538
         Age |   -.114241   .1227597    -0.93   0.352    -.3548456    .1263636
       _cons |  -3.357176   .6080281    -5.52   0.000    -4.548889   -2.165463
------------------------------------------------------------------------------
```

Figure 8: A saturated logistic regression model, built to derive a final model through stepwise backward regression analysis

```
. logit  Mortality STAT2020_score Age

Iteration 0:   log likelihood = -47.745809
Iteration 1:   log likelihood = -45.903483
Iteration 2:   log likelihood = -44.816492
Iteration 3:   log likelihood = -44.809873
Iteration 4:   log likelihood = -44.809855
Iteration 5:   log likelihood = -44.809855

Logistic regression                               Number of obs =     242
                                                  LR chi2(2)    =    5.87
                                                  Prob > chi2   =  0.0531
Log likelihood = -44.809855                       Pseudo R2     =  0.0615

------------------------------------------------------------------------------
   Mortality | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
STAT2020_sc~e|   1.261616    .697345     1.81   0.070    -.1051552    2.628387
         Age |  -.1237151    .123521    -1.00   0.317    -.3658119    .1183817
       _cons |  -3.257578   .5848614    -5.57   0.000    -4.403885   -2.111271
------------------------------------------------------------------------------
```

Figure 9: Stepwise backward univariate analysis regression excluding morbidity

To demonstrate the logistic regression analysis, a saturated model (model with all variables: morbidity, mortality risk score and age, predicted mortality) was developed. Using a flexible *p*-value of 0.25, the non-predictive variables were dropped out. This is often called a univariate logistic regression analysis.[10]

An important first observation of the model in Figure 8 is that it is not a statistically significant model. The univariate analysis principle, as discussed in Sperandei, would suggest that variable age be dropped out first.[10] Age has the highest *p*-value of 0.35, which is greater than the recommended 0.25 suggested by Sperandei.[10] The *p*-value of 0.25 is not a rigid selection, as the intention of the regression at this stage is not to predict relationships but rather to select candidate predictors.[10] Based on this notion, age was kept in the model at the first backward dropping of predictors. Morbidity was the initially excluded predictor as in Figure 9.

Figure 9 still reflects an insignificant model, but the *p*-value has improved to what some researchers might term marginally significant. In this paper, even if the *p*-value is above 0.05 by a small fraction of a number, it was considered insignificant. The Figure 9 model still has age as highly insignificant (*p*-value of 0.32). Therefore, in the second iteration of model building, in the direction that removes insignificant variables, age was omitted in the next model.

The iterations in Figure 10 (4 iterations) indicate how rapidly the modelling process converged. The model had a log-likelihood of -45.60, which is a measure of the goodness-of-fit (GOF). It can range from negative infinity to positive infinity. The bigger the log-likelihood of a model is, the better the model. However, it is often not a used indicator, unless it is used to help compare nested models.

The model without the two highly insignificant variables (age and morbidity), is a significant model. The likelihood ratio chi-square has a significant *p*-value. This indicates that adding the variable surgical risk of mortality score made the model predict mortality better than the null model (a model with just the intercept). However, it is possible that in practice a reduced model may exclude some variables that have clinical relevance. Therefore, the determination to identify a model as final should always weigh in the clinical relevance of the factors studied for the outcome of interest. For the current paper, the model in Figure 10 was accepted as the final logistic regression model. Figure 11 represents the final model with odds ratios. To have the confidence that the selected model is indeed the best, a LR test with a null hypothesis can be computed to establish if the models are statistically different (significantly different based on the null hypothesis that the full model is the same as the reduced model).

```
. logit  Mortality  STAT2020_score

Iteration 0:   log likelihood = -47.847097
Iteration 1:   log likelihood = -46.597586
Iteration 2:   log likelihood = -45.577526
Iteration 3:   log likelihood = -45.576949
Iteration 4:   log likelihood = -45.576949

Logistic regression                                     Number of obs =    244
                                                        LR chi2(1)    =   4.54
                                                        Prob > chi2   = 0.0331
Log likelihood = -45.576949                             Pseudo R2     = 0.0474

------------------------------------------------------------------------------
   Mortality | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
STAT2020_score |   1.514173   .6632878     2.28   0.022     .2141525    2.814193
       _cons |  -3.677442   .4858115    -7.57   0.000    -4.629615   -2.725269
------------------------------------------------------------------------------
```

Figure 10: Final significant model, presented with the coefficients that need to be exponentiated to get the odds ratios

```
. logit, or

Logistic regression                                     Number of obs =    244
                                                        LR chi2(1)    =   4.54
                                                        Prob > chi2   = 0.0331
Log likelihood = -45.576949                             Pseudo R2     = 0.0474

------------------------------------------------------------------------------
   Mortality | Odds ratio   Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
STAT2020_score |   4.545659   3.01508     2.28   0.022     1.238812    16.67971
       _cons |   .0252876   .012285    -7.57   0.000     .0097585    .0655285
------------------------------------------------------------------------------
Note: _cons estimates baseline odds.
```

Figure 11: Final model with odds ratios and their 95% confidence interval (CI)

For the model in Figure 11, for every one-unit change in the STAT 2020 mortality risk score, the log odds of mortality (versus survival) increased by 4.55. The final model equation is:

log(p/1 - p) = 0.25 + 4.545659*STAT2020score

To test the quality of the model, there are a few techniques to establish the prediction error of the model. A useful technique is the training and testing approach, where the data can be subset with a bigger portion, often 70% used to develop the model in a process called training, and the rest of the data are used to validate the model in a process called testing.[13] Another method is the use of the area under the receiver operating characteristic curve (ROC curve). Additional methods include computation of a confusion matrix, using GOF tests (Pearson GOF and the Hosmer-Lemeshow GOF tests), information criteria statistics, which are also a form of GOF tests, and analysis of residuals following the model command.[13]

The vertical line in Figure 12 can be taken as a model that has no predictive value. A model with a high predictive value has an area under the ROC curve that approximates or goes closer to 1. The current model has an area under the ROC curve of 0.71. A ROC curve of 0.72 is often described as representative of a strong model, and the current model nearly achieved that level of predictive value.

Figure 13 represents the result of a Pearson GOF test. The null hypothesis is that there is no difference in the number of observed and predicted successes in each group of the outcome. The *p*-value is significant and therefore we can reject the null hypothesis. This test statistic corrodes the confidence that regression has achieved good agreement between the model predictions and the observed mortality outcomes.

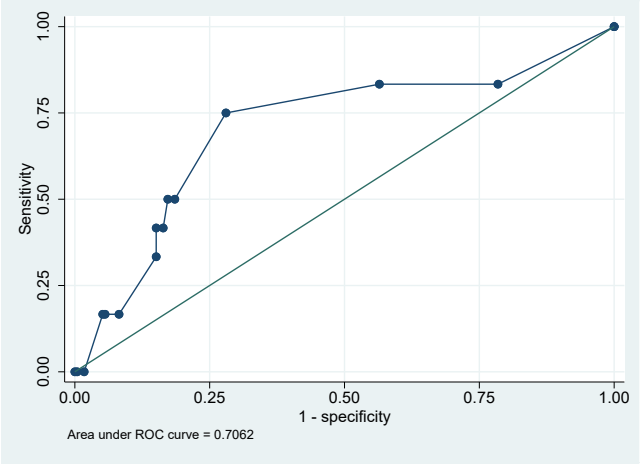

Figure 12: ROC curve for the final logistic regression model

```
. estat gof

Goodness-of-fit test after logistic model
Variable: Mortality

      Number of observations =    244
Number of covariate patterns =     14
           Pearson chi2(12) =  24.97
               Prob > chi2 = 0.0150
```

Figure 13: A GOF test statistic with a significant *p*-value

```
. estat class

Logistic model for Mortality

                 True
Classified |         D          ~D |     Total
-----------+----------------------+----------
         + |         0           0 |         0
         - |        12         232 |       244
-----------+----------------------+----------
     Total |        12         232 |       244

Classified + if predicted Pr(D) >= .5
True D defined as Mortality != 0
--------------------------------------------------
Sensitivity                     Pr( +| D)   0.00%
Specificity                     Pr( -|~D)  100.00%
Positive predictive value       Pr( D| +)      .%
Negative predictive value       Pr(~D| -)  95.08%
--------------------------------------------------
False + rate for true ~D        Pr( +|~D)   0.00%
False - rate for true D         Pr( -| D)  100.00%
False + rate for classified +   Pr(~D| +)      .%
False - rate for classified -   Pr( D| -)   4.92%
--------------------------------------------------
Correctly classified                       95.08%
--------------------------------------------------
```

Figure 14: A confusion matrix for the logistic regression model

Although a confusion matrix is one of the most popular post-regression tests, the results can be affected by the proportion of the outcome in the sample or the positive cases.[14] This problem was a reality for the current model developed using data that was computer generated and might not represent real-life patient data. However, the data worked well to demonstrate the concepts. This limitation can be addressed by earlier steps of considering the representation of the outcome in the sampling techniques and calculations. Figure 14 reports the indicators in the confusion matrix.

Whether the data types favour linear regression analysis or logistic regression analysis, the process of data collection, data preprocessing, and finally deciding on the correct regression analysis to be performed require diligence and careful understanding of the statistical assumptions associated with the chosen analysis.

Conclusion

Regression analysis is a powerful tool that enables researchers and analysts to uncover relationships, identify trends, and make predictions. If adequate data is used correctly, studied relationships using regression analysis can provide insights about the phenomena in question. Simple linear and multiple linear regression can be used successfully to understand health data that is continuous, but when data of interest has dependent variables that are binary or categorical, a linear regression analysis will be incorrect. The logistic regression can adequately analyse data where the outcome is binary. It is important to perform post-model testing to ensure the quality of the regression model. This quality assurance will enhance the usefulness of the insights derived from regression analysis and modelling.

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References

1. Arnab R. Survey sampling theory and applications. Academic Press; 2017. p. 673-89. https://doi.org/10.1016/B978-0-12-811848-1.00020-0.
2. Olsson U. Generalized linear models: an applied approach. Professional Pub Service; 2002. p. 18.
3. Kumar S, Bhatnagar V. A review of regression models in machine learning. J Intell Inf Syst. 2022;3(1):40-7.
4. Marill KA. Advanced statistics: linear regression, part ii: multiple linear regression. Acad Emerg Med. 2004;11(1):94-102. https://doi.org/10.1197/j.aem.2003.09.006.
5. Gujarati DN. Basic econometrics. 4th ed. New Delhi: Tata McGraw-Hill; 2004.
6. Jacobs ML, Jacobs JP, Thibault D, et al. Updating an empirically based tool for analyzing congenital heart surgery mortality. World J Pediatr Congenit Heart Surg. 2021;12(2):246-81. https://doi.org/10.1177/2150135121991528.
7. Kebalepile MM, Chakane PM. Commonly used statistical tests and their application. South Afr J Anaesth Analg. 2022:S80-S4.
8. Howson C. The curious case of Frank Ramsey's proof of the multiplication rule of probability. Analysis. 2018;78(3):431-9. https://doi.org/10.1093/analys/anx161.
9. Pandis N. Logistic regression: part 1. Am J Orthod Dentofacial Orthop. 2017;151(4):824-5. https://doi.org/10.1016/j.ajodo.2017.01.017.
10. Sperandei S. Understanding logistic regression analysis. Biochem Med (Zagreb). 2014;24(1):12-8. https://doi.org/10.11613/BM.2014.003.
11. Bujang MA, Sa'at N, Sidik TMITAB, Joo LC. Sample size guidelines for logistic regression from observational studies with large population: emphasis on the accuracy between statistics and parameters based on real life clinical data. Malays J Med Sci. 2018;25(4):122-30. https://doi.org/10.21315/mjms2018.25.4.12.
12. Van Smeden M, Moons KG, de Groot JA, et al. Sample size for binary logistic prediction models: beyond events per variable criteria. Stat Methods Med Res. 2019;28(8):2455-74. https://doi.org/10.1177/0962280218784726.
13. Dankers FJWM, Traverso A, Wee L, van Kuijk SMJ. Prediction modeling methodology. Springer International Publishing; 2019. p. 101-20. https://doi.org/10.1007/978-3-319-99713-1_8.
14. Fielding AH, Bell JF. A review of methods for the assessment of prediction errors in conservation presence/absence models. Environ Conserv. 1997;24(1):38-49. https://doi.org/10.1017/S0376892997000088.

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FCA REFRESHER COURSE

The physics of ultrasound and Doppler

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Keywords: ultrasound, Doppler, physics

Introduction

Ultrasound imaging is an important diagnostic and intervention tool that incorporates high-frequency sound waves to generate images. The Doppler effect, and the different Doppler modalities, form an essential component of ultrasound, enabling the measurement of blood flow velocity and direction. In this article, we will delve into the physics behind ultrasound and Doppler and explore the underlying principles that make these technologies possible.[1]

Sound waves

Waves carry energy from one location to another and may present in the form of sound, heat, magnetic, or light energy. As sound travels through a medium, it results in the vibration of molecules, creating high-pressure compressions and low-pressure rarefactions.[1] Sound travels through a medium in a straight line, which can be represented as a sine wave, as shown in Figure 1.[2]

The definition of ultrasound is the vibration of sound at a frequency above the threshold of human hearing. Table I depicts the speed of sound travelling through different media. Medical ultrasound imaging typically uses sound waves at frequencies of 1–20 megahertz (MHz). Sound wave properties are described in terms of frequency/Hertz (Hz), wavelength (mm), amplitude (dB), power (Watt), intensity (Watt/square cm), period (ms), and propagation velocity (m/s). These properties are depicted in Figure 1 and can be defined as follows:

- Frequency refers to the number of repetitions or sound wave cycles per second and the speed of the sound wave/wavelength (frequency and wavelength are inversely proportional).[1] The speed of sound through soft tissue is 1 540 m/s.[3]
- Wavelength is the distance between excitations or the length of a single wave cycle.
- Amplitude or loudness of the excitation is the energy of the sound wave.[1]

Sound waves, and the media through which they travel, undergo different interactions. The resistance to ultrasound propagation is referred to as acoustic impedance and depends on the medium's density and the speed at which sound travels through

Table I: Speed of sound through different media[1]

Tissue type	Speed (m/s)
Air	330
Lung	500
Fat	1 450
Liver	1 560
Blood	1 560
Muscle	1 600
Tendon	1 700
Bone	3 500
Soft tissue (average)	1 540

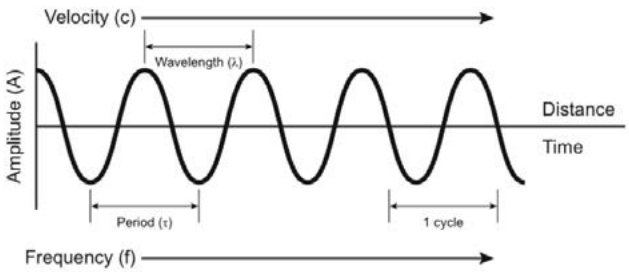

Figure 1: Different aspects of a wave[1]

that particular medium.[1] Ultrasound waves encounter interfaces between two different tissue media and may undergo reflection, transmission, absorption, attenuation, scattering, refraction, and diffraction.[1,3] These terms can be defined as follows:

- Reflection occurs when waves bounce back at the interface. The greater the difference in acoustic impedance across a tissue boundary, the more ultrasound will be reflected.
- Transmission happens when the waves pass through the interface.
- Absorption occurs with the conversion of ultrasound energy to heat.
- Attenuation refers to the reduction in intensity and amplitude of the ultrasound waves as they move through a medium and energy is lost. Attenuation is caused by absorption, scattering, and divergence. Different tissues and media have different attenuation coefficients, enabling the detection of structural

differences in ultrasound imaging. Echoes are generated when ultrasound waves encounter tissue interfaces. These echoes are received by the transducer and converted into electrical signals and images.[1]

- Scattering occurs when ultrasound beams strike an object at right angles and are scattered in all directions. If the tissue has an irregular border, the beams will not be returned to the transducer and most of the energy is lost to surrounding tissues.
- Refraction refers to a sound wave's change in velocity through media with different acoustic impedance, resulting in a change in the direction of the ultrasound wave.
- Diffraction refers to the spreading out of a beam as it moves farther from the ultrasound source and as the intensity of the ultrasound beam decreases.

Ultrasound probes and the piezoelectric effect

Ultrasound transducers consist of piezoelectric crystals (e.g. lead zirconate titanate) that convert electrical energy into sound waves and sound waves back into electrical energy. When an alternating current is applied to the transducer, the ultrasound crystals deform and produce ultrasound waves. The piezoelectric effect is the vibration of a piezoelectric crystal at the tip of the transducer that generates a specific ultrasonic frequency to create ultrasound waves. The ultrasound waves penetrate the propagation medium and are reflected to return to the transducer. The transducer then converts the returning ultrasound waves to electrical energy, which can be interpreted as an image on the ultrasound machine.[1,2]

Image quality is determined by tissue resolution (the ability to distinguish two objects that are spatially close together) and penetration. High-frequency probes have decreased penetration because the piezoelectric crystal can only send out a limited number of ultrasound waves before the waves dissipate.[1] Probes that emit higher frequencies and lower wavelengths result in better resolution but compromised penetration.[3] Table II depicts the properties of the different ultrasound probes.

Table II: Properties of the different ultrasound probes[3]

Transducer type	Phased array	Linear	Curvilinear
Frequency	1–5 MHz	5–10 MHz	2–5 MHz
Depth	35 cm	9 cm	30 cm
Applications	Heart, lungs	Abdominal, pelvic	Arteries, veins, musculoskeletal, eyes, and testes

Imaging modes

Ultrasound systems offer different imaging modes, each with unique capabilities and applications.

A-mode (amplitude mode)

This displays a single echo signal against time to measure depth.[1] It is rarely used in today's clinical practice.

B-mode (brightness mode)

B-mode ultrasound is the most used mode in diagnostic ultrasound. B-mode imaging uses the amplitude of the received ultrasound echoes to represent different shades of grey on the image. This allows for the visualisation of different tissues and structures. B-mode provides two-dimensional (2D) images and has a wide range of applications.[2]

M-mode (motion mode)

M-mode ultrasound is a specialised mode that displays a one-dimensional (1D) representation of motion over time. It is primarily used to assess dynamic structures, such as cardiac motion. In M-mode imaging, a single ultrasound beam is continuously transmitted at a fixed location. This generates a real-time image of motion along a selected scan line.[2]

Three-dimensional (3D) and four-dimensional (4D) ultrasound modes

3D and 4D ultrasound modes provide a more comprehensive view of anatomical structures. 3D imaging captures multiple 2D slices of a region, which are then reconstructed to form a 3D volume. 4D imaging adds real-time motion to 3D imaging, which allows for the visualisation of dynamic parameters and structures.[1]

Doppler mode

Doppler ultrasound is an ultrasound mode that utilises the Doppler effect to measure the velocity and direction of blood flow. It provides information about blood flow patterns, and valvular pathology, enabling the assessment of haemodynamic parameters. Doppler ultrasound can be further classified into colour and spectral Doppler.[1]

Colour Doppler imaging incorporates the overlaying of colour-coded representations of flow information onto the B-mode image. This allows for the visualisation of blood flow direction and velocity. Different colours (e.g. red and blue) represent flow towards and away from the transducer.[1,2]

Spectral Doppler provides quantitative information about blood flow velocities. It displays the Doppler frequency spectrum as a graph, known as the Doppler spectrum or waveform. Spectral Doppler is used in the evaluation of cardiac function.[2]

The Doppler effect

The Doppler principle is a fundamental concept in physics also applied in medical imaging, such as ultrasound. In ultrasound, the Doppler effect enables the measurement of blood flow velocity and direction. The Doppler principle was named after Christian Doppler. It describes the change in the frequency of a

sound wave when the source or observer is in relative motion to one another.[2,3] This shift in the frequency of the wave is known as the Doppler frequency shift. The frequency shift is directly proportional to the velocity.

In medical practice, the frequency shift occurs when ultrasound waves encounter moving blood cells and the frequency of the reflected waves changes. The ultrasound will pick up this shift in frequency. If an object moves toward the transducer, the frequency increases (positive Doppler shift), while movement away from the transducer results in a decreased frequency (negative Doppler shift).[1,2] The Doppler principle can further be explained using the wave equation. When a wave source and an observer are in motion relative to each other, the observed frequency differs from the emitted frequency according to the equation set out below.[1]

Doppler equation

The Doppler equation relates the observed frequency shift to the velocity of the moving blood cells, the speed of sound in tissue, and the angle between the ultrasound beam and the direction of blood flow. The equation is given by:

$\Delta f = 2 \times f \times V \times \cos a / c$

Where:

Δf = Doppler frequency shift (Hz)

f = ultrasound frequency (Hz)

V = velocity of blood flow (m/s)

d = direction of blood flow relative to the ultrasound beam = cos a (Cosine of the angle between blood flow direction and ultrasound beam.)

c = speed of sound in tissue (1 540 m/s)

The sign convention depends on whether the observer and source are moving toward each other or away from each other.

Continuous wave (CW) Doppler

CW Doppler utilises two separate ultrasound transducers. One transducer is used for transmitting and the other for receiving. This allows for continuous emitting and detecting of sound waves. The frequency shift is measured along the entire ultrasound beam. This provides information about blood flow velocity along the entire beam and cannot identify its location. CW Doppler is commonly used in cardiovascular applications requiring measurement of high velocities.[1,2]

Pulsed wave (PW) Doppler

PW Doppler employs a single transducer that alternates between transmitting and receiving ultrasound waves. It allows the user to select a specific region of interest and enables depth-specific measurements, thus providing information about blood flow velocity at different locations. PW Doppler is widely used in clinical applications, including obstetrics, cardiology, and vascular imaging, and can measure lower velocities than CW Doppler.[2,3]

Nyquist limit and aliasing

The Nyquist limit is a fundamental concept in Doppler ultrasound that allows for the accurate measurement of blood flow velocity. Understanding the Nyquist limit is essential for ensuring accurate and reliable measurements.[1]

The Nyquist sampling theorem is a fundamental concept in signal processing. To accurately reconstruct a continuous signal, it states that the signal must be sampled at a rate at least twice the highest frequency component present in the signal.[1] This principle applies to Doppler ultrasound as well. According to the Nyquist theorem, the maximum measurable velocity is limited by the ultrasound system's pulse repetition frequency (PRF). The Nyquist limit states that the PRF must be at least twice the maximum Doppler frequency shift to avoid aliasing. The Nyquist limit is the upper limit of detectable velocities without aliasing. Aliasing occurs when the Doppler frequency shift exceeds the Nyquist frequency, leading to an incorrect representation of blood flow velocity.[1] Aliasing is where spectral overlap occurs and manifests as a wrap-around effect. This is where high velocities appear as lower velocities in the opposite direction.[1,2]

Ultrasound system configuration

To avoid aliasing and accurately measure blood flow velocities, the ultrasound system must be appropriately configured. The following considerations are important:

a. Doppler angle correction: The Doppler angle is the angle between the ultrasound beam and the direction of blood flow, and this will affect the measured velocity. As the angle increases, the velocity calculations become more inaccurate.[1]
b. Adjusting scale and baseline: The scale and baseline settings determine the range and zero reference for Doppler velocity measurements. Proper adjustment ensures that the desired velocities are within the detectable range and displayed optimally.[1]
c. Doppler gain optimisation: Doppler gain settings affect the sensitivity of the Doppler system. The gain optimisation allows for the clear visualisation of low-velocity flows and avoids excessive artefacts.[1]
d. Colour Doppler mapping: Colour Doppler provides a visual representation of blood flow direction and velocity. The Nyquist limit should be set appropriately to prevent aliasing. The colour scale should also be adjusted to display the desired range of velocities to be measured.[1]

Conclusion

Ultrasound is sound with a frequency above 20 kHz. The physical properties of sound waves (wavelength, frequency, and velocity) dictate the limits of clinical ultrasound. Ultrasound is generated using piezoelectric materials. The image created is dependent on the physical properties of the tissue being examined as

well as the ultrasound wave and probe properties.[3] Ultrasound is an extremely complex and useful tool and having a good understanding of all the properties and functions thereof will allow one to utilise the platform as accurately as possible.

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References

1. Edelman SK. Understanding ultrasound physics. 4th edition. Texas: E.S.P. Ultrasound; 2011.
2. Fenneck R, Kneeshaw J, Ranucci M. Core topics in transesophageal echocardiography. London: Cambridge University Press; 2010. https://doi.org/10.1017/CBO9780511730238.
3. Otto CM. Textbook of clinical echocardiography. Philadelphia: Saunders; 2013.

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Atypical opioids

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Opiates and opioids remain the main pillars of analgesia. Their use is, however, limited by abuse potential as well as their side effect profile. Thus, there is a need for the development of newer opioids. The atypical opioids tramadol, tapentadol, dextromethorphan (DXM), and buprenorphine are newer synthetic opioids. These opioids do not solely depend on mu-receptor agonism for their analgesic effects. Except for DXM, atypical opioids are now being used more than conventional opioids as part of chronic pain management.

Keywords: atypical opioids, chronic pain management

Introduction

Atypical opioids, also known as synthetic opioids, are a class of opioids that differ from traditional opioids in structure, function, and adverse effects. This class of drug aims to decrease negative opioid effects commonly seen with traditional opiates, like morphine, as well as provide adequate analgesia.[1] This review aims to highlight the pharmacology of atypical opiates such as tramadol, tapentadol, DXM, and buprenorphine. An understanding of traditional opiate pharmacology is imperative as part of our understanding of atypical opiates.

The terms opiates and opioids are used interchangeably but they differ:[2]

1. Opiates are natural opioids, derived from or related to the poppy plant, such as heroin, codeine, and morphine.
2. Opioids are a compound resembling opium, attached to opioid receptors that are partially or fully synthetic, such as fentanyl, hydrocodone, and oxycodone.

Physiology of opioids

Opioid receptors are G-protein-coupled receptors that mediate the body's response to hormones, neurotransmitters, and drugs. Three major receptors were discovered that were designated mu, kappa, and delta. Currently, they are termed mu-opioid receptor (MOR), kappa-opioid receptor (KOR), delta-opioid receptor (DOR), and the nociceptin/orphanin FQ peptide (NOP) receptor. The endogenous ligands for these receptors are the neuropeptides β-endorphin (MOR), dynorphin (KOR), and methionine enkephalin (DOR).[3]

Opioid receptors are located throughout the central nervous system and within peripheral tissue of neural and non-neural origin. Centrally, the periaqueductal grey (PAG), locus coeruleus, rostral ventromedial medulla, and limbic system show high concentrations of opioid receptors. Opioid receptors are also present in the substantia gelatinosa of the dorsal horn of the spinal cord. Peripherally, receptors are distributed in the gastrointestinal tract, nerve fibres vas deferens, knee joints, gastrointestinal tract, heart, and immune system.[3,4]

Classification of opioids[3,4]

There are several opioid classifications. Below are tables highlighting the classification systems either via origin (Table I) or receptor type (Table II).

Table I: Classification of opioids via origin

Naturally occurring compounds	Semi-synthetic compounds	Synthetic compounds
Morphine	Diamorphine	Fentanyl, alfentanil, remifentanil
Codeine	Dihydromorphone	Methadone
Thebaine	Oxycodone	Pethidine
Papaverine	Buprenorphine	Tramadol
		Tapentadol

Table II: Classification of opioids via receptor action

Agonists	Morphine, pethidine, fentanyl, sufentanil, remifentanil, alfentanil, oxycodone
Antagonists	Naloxone, methylnaltrexone, nalmefene
Mixed agonists-antagonists (dualists)	Buprenorphine, pentazocine, nalbuphine
Atypical	Tramadol, tapentadol, DXM

Morphine – the prototype opiate

Morphine is considered the prototype opiate against which other agents are measured for their analgesic effects as well as adverse side effects. The effects of opiates and opioids are often compared to morphine for analgesic potency, side effect profile, as well as dependency or abuse potential.

Morphine is a mu-agonist administered orally, intravenously, or intramuscularly. Metabolism is via the liver, where it undergoes

extensive first pass metabolism to morphine-3-glucuronide (less potency) and morphine-6-glucuronide (increased potency compared to morphine).[4]

Uses include analgesia, cough suppression, sedation, anti-diarrhoeal, and perioperative analgesia.[4]

The side effect profile is important because other opiates are compared to morphine. The side effects include somnolence, nausea, vomiting, constipation, pruritus, hypotension, and bradycardia.[4] Abuse potential is high with the naturally occurring opiates.

Atypical opioids

The atypical opioids show different profiles compared to conventional opioids with regard to efficacy, safety, tolerability and risk of abuse. These include Tramadol, DXM, tapentadol and buprenorphine and will be discussed below.

Tramadol

Tramadol is the prototype of the atypical opiate family. It is a centrally acting analgesic structurally similar to morphine and codeine. It is a synthetic 4-phenyl-piperidine analogue of codeine. It is a central analgesic with a low affinity for opioid receptors.[5] Its potency is one-tenth that of morphine.[4] Tramadol is available as an intravenous preparation, orally, and in sustained-release formulations.[6]

Structure

The chemical name for tramadol is 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol. Its molecular formula is $C_{16}H_{25}NO_2$ (Figure 1).

Indications

The main indication for tramadol is for perioperative pain or mild to moderate pain. This is usually part of a multimodal strategy. Due to its abuse potential, its use should be limited. The immediate-release formulation is usually reserved for pain lasting less than one week. The sustained-release formulation is reserved for pain that needs 24-hour management.

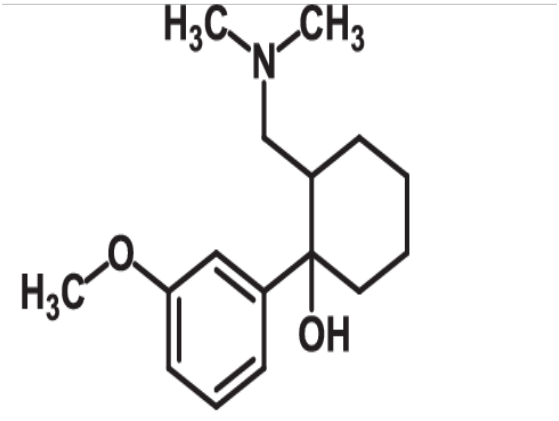


Figure 1: Structure of tramadol[7]

Tramadol may be found in a combination form with paracetamol for additive analgesia.

Off-label indications for tramadol are for restless legs syndrome as well as for the treatment of premature ejaculation. It has also been described for use in anxiety and depression and postoperative shivering.[8]

Mechanism of action[9]

Tramadol differs from traditional opiates. It has a two-fold effect. It works on the mu-receptor as a μ-opioid agonist where it has up to 4 500 times less affinity compared to morphine and affects monoamines by modulating the effects of neurotransmitters involved in the modulation of pain, such as serotonin and noradrenalin, which activate descending pain inhibitory pathways. Tramadol's effects on serotonin and norepinephrine mimic the effects of other serotonin noradrenergic receptor inhibitor (SNRI) antidepressants, such as duloxetine and venlafaxine.

Tramadol exists as a racemic mixture. It consists of two pharmacologically active enantiomers. These contribute to its analgesic property through different mechanisms: (+)-tramadol and its primary metabolite (+)-O-desmethyl-tramadol. The (+)-tramadol inhibits serotonin reuptake, and (-)-tramadol inhibits norepinephrine reuptake. These pathways are complementary and synergistic, improving tramadol's ability to modulate the perception of and response to pain.[9]

Absorption

Tramadol has an oral absorption of 100%, with a mean bioavailability of 70% due to a 20–30% first pass metabolism after a single oral dose. After multiple oral dosing, the bioavailability may increase by 90–100%, which may be the result of a saturated first pass hepatic metabolism. The bioavailability of tramadol after food intake, although increased, does not seem to be clinically relevant.[9]

Distribution[8]

Tramadol has a volume of distribution of approximately 2.7 L/kg and is only 20% bound to plasma proteins.

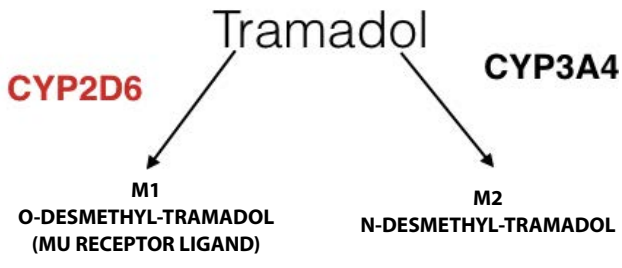
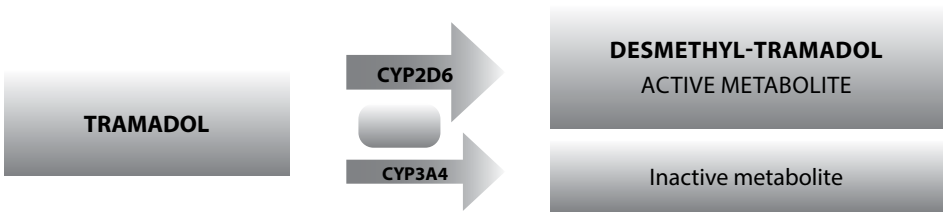


Figure 2: Hepatic metabolism of tramadol (cytochrome pathway)
CYP2D6 – cytochrome P2D6, CYP3A4 – cytochrome P3A4



CYP2D6 ultra-rapid metaboliser – increased concentration of desmethyl-tramadol – increased side effects
CYP2D6 poor metaboliser – lower concentration of desmethyl – tramadoldecreased analgesia

Figure 3: Pharmacogenomics of tramadol

Metabolism and elimination[9]

Tramadol is extensively metabolised in the liver by *O*- and *N*-demethylation and by conjugation reactions to form glucuronides and sulfate metabolites. The *O*-demethylation of tramadol to its main active metabolite, *O*-desmethyl-tramadol (M1), is catalysed by cytochrome P450 (CYP) 2D6 and N-desmethyl-tramadol is catalysed by the enzyme CYP3A4 (Figure 2).

Pharmacokinetic-pharmacodynamic characterisation of tramadol is difficult because of the differences between tramadol concentrations in the plasma and at the site of action, and because of the pharmacodynamic interactions between the two enantiomers of tramadol and its active metabolites.[9]

The major route of excretion for tramadol and its metabolites is through the kidneys. About 30% of the dose is excreted in the urine as the parent drug and the rest are excreted as metabolites.[9]

Pharmacogenomics of tramadol[9]

CYP2D6 is one of the major CYP450 enzymes in drug metabolism via the liver. CYP2D6 converts tramadol to its more active metabolite, *O*-desmethyl-tramadol (Figure 3). Therefore, alterations in the metabolism of tramadol have a profound impact on the analgesic effect and risk of side effects. There have been reports of life-threatening respiratory depression in children who received tramadol following tonsillectomy and/or adenoidectomy, due to the ultra-rapid metabolism of tramadol caused by a CYP2D6 polymorphism. The Food and Drug Administration (FDA) has placed a black box warning on the use of tramadol in children younger than 12 years old and in patients who have other risk factors that may increase sensitivity to the respiratory depressant effects of the drug.

Dosage[4]

Oral formulations are dosed like intravenous formulations.

The different formulations include oral 50 mg capsules or oral 20 drops, equal to 50 mg, sustained release (between 50–200 mg tablets and 100 mg suppositories for adults, and 15–50 mg for paediatric patients).

Suppositories are not available in South Africa. Tramadol can be used in a parenterally controlled pump. Doses suggested include a loading dose of 3 mg/kg followed by a bolus of 20–30 mg/kg and a lockout time of 10 minutes.[4]

Adverse effects

Between 1997 and 2017, there were 730 tramadol cases reported to the FDA's Adverse Event Reporting System. Seizures and serotonin syndrome accounted for 7% and 3% of the cases, respectively.[10]

Side effects are dose dependent. Nausea and vomiting are problematic on tramadol along with commonly reported side effects such as headache, somnolence, dyspepsia, sweating (due to monoaminergic effects), dry mouth, and postural hypotension.[4]

Serious adverse effects include respiratory depression. Adolescents aged 12–18 years may have additional risk factors for respiratory depression, obstructive sleep apnoea, obesity, severe lung disease, and neuromuscular disease.[6,10]

Serotonin syndrome occurs due to the inhibition of adrenalin and serotonin by tramadol in the central nervous system. Patients on monoamine oxidase inhibitors, serotonin-releasing drugs, and serotonin reuptake inhibitors should not be prescribed tramadol. They are at increased risk of serotonin syndrome. The classic triad of symptoms includes neuromuscular hyperactivity, autonomic hyperactivity, and altered mental status. Complications from serotonin syndrome include rhabdomyolysis, myoglobinuria, renal failure, disseminated intravascular coagulation, metabolic acidosis, and acute respiratory distress syndrome.[11]

Toxicity can also predispose patients to seizure activity and cardiac dysrhythmias, such as prolongation of the QT interval.[9]

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome.

An overdose of tramadol leads to respiratory depression and seizures. Naloxone can be used to treat respiratory depression or tramadol-induced apnoea. A recent meta-analysis showed that naloxone administration does not increase the risk of seizure in patients with tramadol toxicity. Seizures due to tramadol do not respond to naloxone but are relieved with benzodiazepines. A combination of diazepam/naloxone is reported as an efficient antidote to reverse tramadol-induced central nervous system toxicity.[12] Table III highlights usage of tramadol in special

populations including paediatrics, renal and hepatic dysfunction, geriatric usage, pregnancy and breastfeeding.

Table III: Tramadol use in special populations

Special population	Precaution
Paediatrics	Off-label drug use can cause respiratory depression. Controversial in children < 12 years old.
Renal dysfunction	Creatinine (Cr) clearance < 30 ml/min, increase dosing interval to 12 hours.
Hepatic dysfunction	A dosing interval of 12 hours is recommended.
Geriatrics	If aged > 75 years, a maximum daily dose of 300 mg.
Pregnancy/ breastfeeding	May be teratogenic and cause somnolence or withdrawal in neonates if taken during breastfeeding.

Tapentadol

Tapentadol is a synthetic, centrally acting atypical opiate with both opioid and non-opioid mechanisms of action; mu-opioid receptor agonist and noradrenaline reuptake inhibition. As an active compound and not a prodrug, it is not reliant on enzyme systems and it is also devoid of active metabolites. It was developed in the 1980s to address the adverse effects associated with tramadol's serotonin reuptake inhibition.[13]

Structure

Tapentadol is a unique, centrally acting opioid of the aromatic hydrocarbon benzenoid class with a chemical formula of $C_{14}H_{23}NO$ (Figure 4).[14]

Mechanism of action[14]

Tapentadol is a non-racemic molecule and is not a prodrug. It is a synthetic opioid that is centrally acting. It has a two-fold analgesic action:

1. Selective mu-opioid receptor agonist (greater affinity than for delta and kappa receptors).
2. Increases noradrenaline levels by inhibiting noradrenaline uptake and activating alpha-2 receptors.

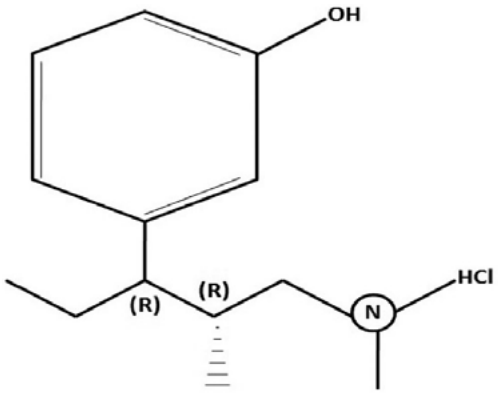


Figure 4: Structure of tapentadol

Tapentadol is a weak serotonin reuptake inhibitor; however, this action does not contribute to its analgesic effect.

Indications[13]

The indications of tapentadol include acute pain, chronic pain, as well as neuropathic pain, especially in diabetic neuropathy. It has also been used in cancer pain. Similar to tramadol, there is a risk of abuse potential with tapentadol. In this regard the tablet is difficult to crush, decreasing the ability to use it for recreational purposes.

Absorption and distribution[13]

The mean absolute bioavailability is 32% due to extensive first pass metabolism. Maximum serum concentrations of tapentadol are typically observed at around 1.25 hours after dosing. Dose-proportional increases in the C_{max} and area under the curve (AUC) values of tapentadol occur over the 50–150 mg dose range. Tapentadol may be given with or without food. The plasma protein binding of the drug is approximately 20%. Thus, the potential for drug interactions is less and the volume of distribution is 540 ± 9.8 L/kg.

Metabolism and elimination[13]

Tapentadol metabolism mainly occurs via the liver via phase II pathways. A very small amount is metabolised via phase I pathways. Therefore, unlike tramadol, the CYP pathway plays a very limited role in tapentadol metabolism. Tapentadol is mainly metabolised via conjugation with glucuronic acid to glucuronides. In the urine, 70% is excreted as O-glucuronide and sulfate metabolites.

Tapentadol is also metabolised via the CYP2C9 and CYP2C19 pathways where demethylation to form N-desmethyl-tapentadol occurs. Approximately 2% of tapentadol undergoes CYP2D6-mediated hydroxylation to form hydroxy-tapentadol. The metabolites of tapentadol are not pharmacologically active. The terminal half-life is about four hours after oral administration. The extended-release formulation has a mean terminal half-life shown to range between 4.4 and 5.9 hours.

Dosage[13]

Tapentadol is available in extended or immediate-release formulations at doses of 50, 75, or 100 mg formulations. Limited evidence exists for its intravenous use; however, it has been used via the intravenous route. In mild renal or hepatic impairment, no dose adjustment is required and the drug should be avoided in severe renal or hepatic impairment. In the elderly, first look at the renal function and dose accordingly and as conservatively as possible.

Adverse effects[13]

Tapentadol produces peripheral and central side effects. Peripherally, tapentadol may cause nausea and vomiting. Centrally, it may cause headaches, dizziness, and somnolence.

It is less likely to cause life-threatening situations associated with delirium, neuromuscular rigidity, and hyperthermia when combined with selective serotonin reuptake inhibitors (serotonin syndrome). Tapentadol should be used cautiously in patients with a history of seizures because it reduces the seizure threshold in patients. Serotonin syndrome has been reported when tapentadol is used in combination with serotonergic antidepressants, but less so than with tramadol.

Dextromethorphan (DXM)[14,15]

DXM is the D-isomer of levorphanol, a synthetic analogue of codeine. DXM also contains an alkylated amine adjacent to a cyclohexane ring, a chemical structure similar to dissociative agents like ketamine and phencyclidine. Unlike the other atypical opiates, its mechanism of action is antagonism at the N-methyl-D-aspartate (NMDA) receptor and sigma-1 receptor.

DXM is indicated as a non-sedating antitussive and is being considered as part of a multimodal perioperative opiate-sparing technique for analgesia due to its NMDA antagonism.

The volume of distribution is estimated to be 5–6.7 L/kg.

DXM undergoes metabolism in the liver via cytochrome (CYP2D6) to dextrorphan (primary active metabolite) and 3-methoxymorphinan. The average half-life of the parent compound in therapeutic use is approximately three hours in individuals who are rapid metabolisers, and 30 hours in slow metabolisers, due to genetic polymorphism. DXM and its metabolites, dextrorphan and 3-methoxymorphinan, are almost exclusively renally excreted.[14,15]

DXM is a drug with great abuse potential. Toxicity presents as nausea, vomiting, respiratory depression, seizures, tachycardia, hyperexcitability, psychosis, cerebellar signs, dystonia, blurred vision, and serotonin syndrome.[14,15]

Buprenorphine

Buprenorphine is a mu-opioid receptor agonist and a weak kappa- and delta-opioid receptor antagonist, thus classing it as an opioid dualist (opioid partial agonist-antagonist). It underwent development in the late 1960s. It is a synthetic analogue of thebaine, an alkaloid compound derived from the poppy flower.[16]

Although buprenorphine is traditionally classified as a partial agonist, the notion that it behaves as a full agonist in analgesia (occupying only 5–10% of MOR to obtain the analgesic effect) is widely accepted nowadays.[17]

Indications

Buprenorphine was initially developed for the treatment of opioid use dependency, especially if methadone is contraindicated. It has now become common in the treatment of acute and chronic pain.

The ceiling effect of buprenorphine[17]

Partial agonists show a partial response compared to a full agonist. This manifests as a plateau effect, referred to as a ceiling effect. Consequently, increasing the dosage of a drug is not proportional to its increased pharmacological effect.[17] A ceiling effect is observed in respiratory depression. Therefore, buprenorphine is used for a better side effect profile compared to other opioids, although respiratory depression can occur. Buprenorphine has anti-hyperalgesic properties, most likely due to its kappa-receptor antagonism.

Pharmacokinetics[16,17]

Buprenorphine is metabolised via the liver via the CYP3A4 system. It has poor first pass metabolism with only 10–15% oral bioavailability. This led to the sublingual formulation where bioavailability is similar to intravenous preparations.

Buprenorphine is metabolised to norbuprenorphine via CYP3A4/3A5-mediated N-dealkylation. Buprenorphine and norbuprenorphine both undergo glucuronidation to the inactive metabolites buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, respectively.

Elimination is via the faeces and urine.

The mean elimination half-life of buprenorphine in plasma ranges from 31 to 42 hours.

Adverse effects[16]

Buprenorphine exerts some anticholinergic-like effects and may cause hypotension, QT prolongation, and a lower seizure threshold.

Other side effects of buprenorphine include nausea, vomiting, drowsiness, dizziness, headache, memory loss, sweating, dry mouth, miosis, orthostatic hypotension, sexual side effects, and urinary retention.

Newer atypical opiods in development:

CEBRANOPODOL:[18]

Due to adverse effects like respiratory depression, tolerance and physical dependance with the atypical opioids currently available, cebranopodol is being evaluated as a novel atypical opioid that acts at the mu opioid receptor as well as the nociceptin/orphanin receptor (NOP) with a better side effect profile and less addictive potential. It may in the future become an alternative to all the currently available opioids.

Conclusion

Despite the increase in opioid abuse worldwide, opioids remain an integral part of our analgesia armamentarium. When compared to the opiate prototype, morphine, the atypical opioids and the advent of new drugs in this field aim for fewer adverse effects, a better analgesia profile, and less abuse potential.

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References

1. Schug SA. The atypical opioids: buprenorphine, tramadol and tapentadol. Med Today. 2019;20(1):31-6.
2. Ciarallo C. Chapter 11: opioids. In: Duke J. Anesthesia secrets. 4th ed. Philadelphia: Mosby; 2011. p. 82-9. https://doi.org/10.1016/B978-0-323-06524-5.00011-8.
3. James A, Williams J. Basic opioid pharmacology - an update. Br J Pain. 2020;14(2):115-21. https://doi.org/10.1177/2049463720911986.
4. Shipton EA. Analgesics for acute pain. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 1st ed. Centurion: Medpharm Publications; 2012. p. 550-3.
5. Drayer P, Desmeules J, Collart L. Pharmacologie du tramadol [Pharmacology of tramadol]. Drugs. 1997;53(Suppl 2):18-24. French. https://doi.org/10.2165/00003495-199700532-00006.
6. Grond S, Sablotzki A. Clinical pharmacology of tramadol. Clin Pharmacokinet. 2004;43(13):879-923. https://doi.org/10.2165/00003088-200443130-00004.
7. Cheng H, Song D, Chang Y, Liu H, Qu J. Chlorination of tramadol: reaction kinetics, mechanism and genotoxicity evaluation. Chemosphere. 2015;141:282-9. https://doi.org/10.1016/j.chemosphere.2015.06.034.
8. Dhesi M, Maldonado KA, Maani CV. Tramadol [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 April 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537060/. Accessed23 July 2023.
9. Miotto K, Cho AK, Khalil MA, et al. Trends in tramadol: pharmacology, metabolism, and misuse. Anesth Analg. 2017;124(1):44-51. https://doi.org/10.1213/ANE.0000000000001683.
10. fda.gov [Internet]. FDA Adverse Event Report System; 2018. Available from: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard. Accessed 2 August 2023.
11. Shadnia S, Brent J, Mousavi-Fatemi K, Hafezi P, Soltaninejad K. Recurrent seizures in tramadol intoxication: implications for therapy based on 100 patients. Basic Clin Pharmacol Toxicol. 2012;111(2):133-6. https://doi.org/10.1111/j.1742-7843.2012.00874.x.
12. Lagard C, Malissin I, Indja W, et al. Is naloxone the best antidote to reverse tramadol-induced neuro-respiratory toxicity in overdose? An experimental investigation in the rat. Clin Toxicol (Phila). 2018;56(8):737-43. https://doi.org/10.1080/15563650.2017.1401080.
13. O'Connor J, Russell C, Harris E, Penning J, McVicar J. Tramadol and tapentadol: clinical and pharmacologic review [Internet]. Anaesthesia Tutorial of the Week: Tutorial 407. WFSA; 2019. Available from: https://resources.wfsahq.org/wp-content/uploads/407_english.pdf. Accessed 23 July 2023.
14. Rosenbaum C, Boyer E. Dextromethorphan misuse and poisoning: clinical features and diagnosis [Internet]. Drugbank Online; 2023 Available from: https://go.drugbank.com/drugs/DB00514. Accessed23 July 2023.
15. Jones IA, Piple AS, Yan PY, et al. A double-blinded, placebo-controlled, randomized study to evaluate the efficacy of perioperative dextromethorphan compared to placebo for the treatment of postoperative pain: a study protocol. Trials. 2023;24(1):238. https://doi.org/10.1186/s13063-023-07240-0.
16. Kumar R, Viswanath O, Saadabadi A. Buprenorphine. Treasure Island: StatPearls Publishing; 2023.
17. Infantino R, Mattia C, Locarini P, et al. Buprenorphine: far beyond the "ceiling". Biomolecules. 2021;11(6):816. https://doi.org/10.3390/biom11060816.
18. Ziemichod W, Kotlinska J, Gibula-Tarlowska E, Karkoszka N, Kedzierska E. Cebranopadol as a novel promising agent for the treatment of pain. Molecules. 2022;27(13):3987. https://doi.org/10.3390/molecules27133987.

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FCA REFRESHER COURSE

Neuropsychiatric pharmacology for the anaesthetist

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Neuropsychiatric conditions are placing an increasing burden on healthcare systems around the world, including South Africa. Providing anaesthesia to patients who are treated with neuropsychiatric agents is becoming a regular occurrence. Emphasis needs to be placed on understanding the pharmacological interactions of these various drug classes with anaesthetic drugs. This review includes antidepressants, anti-anxiety, mood stabilisers, and antipsychotics, and highlights new emerging treatments. Within each class, focus is placed on the physiological alterations related to the drug, the drug interactions, and rare but fatal conditions, such as serotonin syndrome (SS) and neuroleptic malignant syndrome.

Keywords: neuropsychiatric pharmacology, neuropsychiatric conditions, pharmacological interaction

Introduction

In South Africa, neuropsychiatric conditions rank third in their contribution to the burden of disease, after acquired immune deficiency syndrome (AIDS) and other infectious diseases.[1] The pharmacology and anaesthetic implications of these drugs in the perioperative setting are often underappreciated.[2]

Antidepressants

Depression is the most common psychiatric disorder affecting up to 40% of South Africans.[3,4] Pharmacological management is aimed at correcting deficiencies of dopamine, noradrenaline, adrenaline, and serotonin within the brain. Antidepressants can be divided into four groups, discussed below.

Tricyclic antidepressants (TCAs)

TCAs are relatively old antidepressants. The dose-dependent side effects of TCAs have decreased their use as antidepressants. They are now more common in the management of chronic pain. Lower dosages are used for analgesia than used to treat depression, hence they have a more favourable side effect profile.[5]

Mechanism

TCAs act on roughly five different neurotransmitter pathways; its antidepressant effect is due to blocking serotonin and noradrenaline reuptake in presynaptic terminals. The other neurochemical pathways include histaminergic and cholinergic systems, which cause a wide range of side effects.[6]

Anaesthetic implications

TCAs cause multiple ECG changes, nonspecific T-wave abnormalities, widening of the QRS complex, prolongation of QT interval, bundle branch block, and other conduction abnormalities. Unstable tachydysrhythmias are usually seen in overdose but also with drugs such as halothane and pancuronium.[6,7]

Exaggerated blood pressure responses can be expected following the administration of indirect-acting vasopressors. Direct-acting drugs such as phenylephrine are recommended to treat hypotension and one should consider avoiding or reducing the dosage of vasopressors and ketamine to avoid this response.[7] Patients may also exhibit exaggerated responses to sedative agents, so consider dosage reduction. Pancuronium, ketamine, pethidine, and adrenaline-containing solutions should be avoided.[7,8] TCAs should be continued in the perioperative period, as abrupt discontinuation risks withdrawal and relapse.[5,7]

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs)

SSRIs are the first-line treatment for depression and anxiety and the most widely prescribed class of antidepressants. This class of antidepressants is highly efficacious, their side effect profile is well tolerated and is relatively safe in overdose.[5,9] SSRIs are indicated not only for depression but also anxiety disorders, eating disorders, menopausal hot flashes, obsessive-compulsive disorders, post-traumatic stress disorder, premature ejaculation, premenstrual dysphoric disorder, and somatic symptom disorder.[2,9]

Mechanism

SSRIs block the presynaptic reuptake of serotonin to allow increased serotonin levels post-synaptically. There are other delayed therapeutic effects including receptor down-regulation and decreased neuronal firing. SSRIs increase the production of neuroprotective proteins and possess anti-inflammatory

properties.[2,9] SNRIs inhibit the reuptake of both serotonin and noradrenaline with minimal direct effects on other neurotransmitters or receptors.

Anaesthetic implications

The SNRIs do not significantly inhibit cytochrome P450 (CYP) enzymes.[8] SSRIs are inhibitors of the CYP2D6 enzyme. This causes altered metabolism of codeine and tramadol to their active metabolites causing inadequate analgesia. Fentanyl, morphine, and oxycodone are more effective.[9] SNRIs can cause tachycardia and hypertension and may require tighter blood pressure control.[8] SSRIs can also affect platelet aggregation, which is worsened by the concomitant use of other anticoagulants.[2,8] There is less evidence for an increased bleeding risk with SNRIs.[8]

SSRIs/SNRIs should not be stopped perioperatively to avoid discontinuation syndrome. Discontinuation syndrome is caused by the abrupt withdrawal of antidepressants and is associated with nausea, abdominal pain, diarrhoea, sleep disturbance, as well as somatic and affective symptoms. This syndrome starts within a few days of cessation and can last up to three weeks. The treatment is the reintroduction of the antidepressant.[6]

Table I: Serotonin Syndrome (SS)[5,9]

Clinical
The Hunter Criteria for SS is a serotonergic agent plus one of the following: Spontaneous clonus. Inducible clonus and agitation or diaphoresis. Ocular clonus and agitation or diaphoresis. Tremor and hyperreflexia. Hypertonia. Temperature above 38 °C and ocular clonus or inducible clonus.
Differential diagnosis
Neuroleptic malignant syndrome. Anticholinergic toxicity. Malignant hyperthermia. Sympathomimetic toxicity. Meningitis or encephalitis.
Treatment
Discontinue serotonergic agents.
Sedate using benzodiazepines. The aim is to eliminate agitation, neuromuscular abnormalities, and elevations in heart rate and blood pressure; titrate dose to effect.
Provide oxygen (maintain $SpO_2 \geq 94\%$), intravenous fluids, and continuous cardiac monitoring.
If benzodiazepines and supportive care fail to improve agitation and abnormal vital signs, give cyproheptadine (serotonin 1_A and 2_A antagonist). Adult dose: 12 mg orally.
Treat patients with temperature > 41.1 °C with immediate sedation, paralysis, and endotracheal intubation. Treat hyperthermia with standard measures. Avoid antipyretics such as paracetamol.
Complications
Metabolic acidosis, rhabdomyolysis, renal impairment, disseminated intravascular coagulation, seizures, coma, and death.

Serotonin Syndrome (SS)

SSRIs/SNRIs are both associated with the risk of SS.[5] This syndrome can occur when serotonin levels increase due to either an increased dosage of SSRI/SNRI or the introduction of a new serotonergic agent. Concomitant use of pethidine, tramadol, pentazocine, and dextromethorphan should be avoided due to the SS risk.[8] SS is a clinical diagnosis and can manifest a wide range of clinical symptoms, from mild tremors to life-threatening hyperthermia and shock.[8,9] See Table I for a summary of SS.

Monoamine oxidase inhibitors (MAOIs)

MAOIs are not common in clinical practice and are reserved for treatment-resistant depression and atypical depression.[8] The development of newer agents such as SSRIs/SNRIs and the severe food and drug interactions have decreased its usage worldwide.[2]

Monoamine oxidase (MAO) exists as two isoenzymes, MAO_A and MAO_B. MAO_A preferentially deaminates serotonin, adrenaline, noradrenaline, and melatonin. MAO_B preferentially deaminates phenylethylamine, phenylethanolamine, tyramine, and benzylamine. Dopamine and tryptamine are deaminated by both isoenzymes.[2] MAOIs can be classified as reversible or irreversible. They can also be classified according to isoenzyme inhibition, namely selective or non-selective. Moclobemide is a selective inhibitor for MAO_A and selegiline is selective for MAO_B.

Mechanism

MAOIs act by inhibiting MAO, increasing the availability of monoaminergic transmitters. Irreversible MAOIs bind and permanently inactivate MAO, leading to prolonged effects.[8]

Anaesthetic implications

The anaesthetic implications are numerous and some are fatal. Patients taking MAOIs are at risk of hypertensive crisis precipitated by indirect sympathomimetics, like ephedrine or ketamine.[7] Direct-acting sympathomimetics, such as phenylephrine, are preferable.[5,7] Exaggerated responses can be expected and dosages need to be titrated due to receptor hypersensitivity.[8]

Pethidine and dextromethorphan must not be used concurrently with MAOIs. They can precipitate a serotonergic crisis due to synergistic inhibition of serotonin reuptake, termed a Type I/ excitatory reaction.[6–8] Opioids such as tramadol, fentanyl, alfentanil, sufentanil, and remifentanil, as well as methadone, have also been associated with perioperative serotonergic toxicity.[2] MAOIs interact with the CYP enzymes, notably CYP3A4 and CYP2C19.[8] Type II/depressive reactions are due to MAO inhibition of hepatic enzymes resulting in enhanced effects of all opioids. These enhanced effects are reversed by naloxone.[6,7] Pancuronium should also be avoided as it releases stored noradrenaline.[8]

The benefits and risks should be weighed when deciding to discontinue MAOIs. Irreversible MAOIs need to be stopped two

weeks before elective surgery. Reversible MAOIs should be discontinued 24 hours before elective surgery.[7,8]

Dietary interactions

MAOIs inhibit the breakdown of dietary amines and eating foods containing tyramine can lead to severe hypertensive crisis. Tyramine is transported via vesicular monoamine transporter (VMAT) into synaptic vessels and displaces noradrenaline, precipitating the hypertensive crisis.[7] Patients using oral MAOIs must adhere to dietary restrictions, avoiding foods such as cheese, sausage meats, and red wine.[2]

Atypical antidepressants

Bupropion

Bupropion is used in the treatment of depression, hypoactive sexual desire disorder, and smoking cessation. The mechanism of action is inhibition of dopamine and noradrenaline reuptake. Patients are at increased risk of seizures and neuroleptic malignant syndrome. There are no precautions needed with the use of adrenaline perioperatively. Bupropion may reduce the effectiveness of codeine and tramadol due to CYP2D6 inhibition.[2,8]

Trazadone

Trazodone blocks serotonin reuptake, histamine, and alpha-1-adrenergic receptors and is used as an antidepressant and a sleep agent. Trazadone can cause QT prolongation, especially in combination with other drugs that have a similar effect. It may impair platelet aggregation, especially in combination with antiplatelet agents. Patients on trazodone are also at risk of excess somnolence, which is more significant with other sedative agents. Trazadone must not be used with MAOIs due to the associated SS risk. Despite these concerns, it can be continued perioperatively.[2,8]

Ketamine

Ketamine acts on multiple receptors, N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), opioid, nicotinic and muscarinic acetylcholine receptors (Ach), gamma-aminobutyric acid (GABA), and monoaminergic receptors.[7] Esketamine, the S-enantiomer of ketamine, is a fast-acting intranasal treatment used in adults with major depressive disorder with or without acute suicidal ideation. Other indications include treatment of refractory migraines and acute agitation. The rapid antidepressant action lasting two weeks is due to the rapid synthesis of neuroprotective proteins and anti-inflammatory effects.[10,11] To avoid ketamine poisoning, patients should be carefully screened for ketamine prescriptions and recreational use to confirm the overall dosage used. High doses cause systemic and pulmonary arterial pressure increases, tachycardia, and respiratory arrest.[8]

Psilocybin

Psychedelic drugs, including psilocybin, N,N-dimethyltryptamine (DMT), and lysergic acid diethylamide (LSD), are being examined as potential psychiatric therapies.[10,12] In South Africa, psilocybin is criminalised in terms of the Drugs and Drug Trafficking Act and the Medicines and Related Substances Act.[13] Psychedelic microdosing is used for the management of depression and it is gaining popularity due to the faster onset action, improved side effect profile, and sustained action after a single administration.[11] In 2019, psilocybin was granted the "FDA Breakthrough Therapy" designation, which is a process designed to expedite the development and review of drugs based on the potential therapeutic benefit of psilocybin for treating depression and anxiety.[10]

Psilocybin is the prodrug of psilocin, the active metabolite. Psilocin is a 5-hydroxytryptamine (5-HT2A) agonist.[12] LSD displays unusual binding and activation of 5-HT2B receptors, which may be associated with drug-induced valvular heart disease.

Anti-anxiety

Benzodiazepines

Benzodiazepines have a wide spectrum of uses due to their sedative, hypnotic, amnesic, anxiolytic, anticonvulsant, and muscle relaxant properties.[2,8] They are used for the initial treatment of panic disorder, generalised anxiety disorder, and insomnia. Benzodiazepines are used in the treatment of SS and perioperative alcohol withdrawal.[7,8]

Remimazolam is a relatively new addition to this class as of 2021. Remimazolam is a rapidly metabolised benzodiazepine with organ-independent elimination and has no active metabolites. It has a more favourable cardiorespiratory side effect profile compared to propofol and midazolam, which may be of benefit in paediatric, geriatric, and obese patients.[8]

Mechanism

Benzodiazepines bind to the alpha (α) and gamma (γ) subunits of the $GABA_A$ receptor. This binding site is different from the binding of endogenous GABA, which binds between the α and beta (β) subunits. Anxiolysis is associated with greater relative affinity for the α2 subunit.[2,8]

Anaesthetic implications

Benzodiazepines have sedative effects that are additive with other sedative agents and opioids; a dosage reduction may be appropriate. Even though many benzodiazepines are metabolised by CYP3A4, they are not strong inducers or inhibitors.[2] Emergence agitation occurs more commonly after benzodiazepine premedication and in patients with long-term benzodiazepine use. Paradoxical reactions are rare (< 1%) and may be caused by genetically heterogeneous $GABA_A$ receptors and alcohol use. The abuse potential of benzodiazepines is an important consideration for anaesthetists.[8] Perioperative

benzodiazepine use is associated with persistent benzodiazepine use in the postoperative period.[14] The American Geriatric Society also recommends avoiding benzodiazepines in elderly patients for the treatment of insomnia due to the risks of cognitive impairment and falls. Similar consideration should be taken for their use in the perioperative period.[8]

Mood stabilisers

Lithium

Lithium is the third element of the periodic table and exists as a monovalent cation. It interferes with other univalent ions, iodine, sodium, potassium, and hydrogen.[2,7]

Mechanism

Lithium affects multiple molecular pathways. Lithium affects sodium transport in nerve and muscle cells and inhibits inositol monophosphate, decreasing inositol and affecting adrenergic, serotonergic, and cholinergic signalling. It is not metabolised and is renally excreted.[2,8]

Anaesthetic implications

Lithium inhibits the release of thyroid hormones and can result in hypothyroidism. Perioperative thyroid function testing is essential for patients taking lithium.[7] Lithium prolongs the duration of action of both depolarising and non-depolarising neuromuscular blocking agents. Neuromuscular monitoring is recommended in all patients taking lithium. Due to lithium's exclusive renal excretion, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin-converting enzyme inhibitors can all increase serum lithium levels. Similarly, renal dysfunction and dehydration cause lithium levels to rise dramatically.[6] Toxicity occurs when levels are > 1.5 mmol/l and manifests with altered mental state, ataxia, arrhythmias, renal impairment, and coma. Management is supportive with hydration to enhance lithium excretion, discontinuation of lithium, and avoidance of diuretics.[5,6] Lithium should be discontinued at least 48–72 hours before surgery and is safe to discontinue abruptly.[8]

Anticonvulsants

Table II summarises the anaesthetic implications of a patient treated with anticonvulsant agents for mood disorders.

Antipsychotics

Antipsychotic drugs used are classified into two groups, neuroleptic and typical antipsychotics, which cause extrapyramidal side effects like acute dystonia, akathisia, parkinsonism, and tardive dyskinesia. Atypical antipsychotics do not tend to cause extrapyramidal side effects.

Mechanism

They act via dopamine 2 receptor blockade but also act on other receptors like histamine, serotonin, acetylcholine, and alpha-adrenergic receptors.

Anaesthetic implications

Antipsychotics potentiate the sedative and hypotensive effects of anaesthetic drugs. However, patients should continue their antipsychotics preoperatively as abrupt withdrawal may result in the recurrence of psychotic symptoms.[6] Drugs with antidopaminergic effects, such as metoclopramide and prochlorperazine, increase the risk of extrapyramidal side effects

Table II: Summary of anticonvulsants used to treat mood disorders[2,5,8]

Valproic acid	
Mechanism	**Anaesthetic implications**
Increased GABAergic transmission, reduced protein kinase C activity, and inositol cycling.	Continue in the perioperative period. Highly protein-bound and competitive inhibition of CYP3A4 causes increased levels of propofol. Recommended preoperative screening for bleeding risk: • Platelet count. • Bleeding time. • PT and activated partial thromboplastin time. • Fibrinogen and von Willebrand levels.
Carbamazepine	
Mechanism	**Anaesthetic implications**
Binding and inactivation of voltage-gated sodium channels.	Carbamazepine can be continued perioperatively. Strong CYP enzyme inducer. Aminosteroid neuromuscular blocker duration of action is shortened, more frequent dosing or a higher dose may be needed. Decrease plasma concentration of amiodarone, beta blockers, and calcium-channel blockers. Increased metabolism of midazolam, alfentanil, fentanyl, methadone, and tramadol.
Lamotrigine	
Mechanism	**Anaesthetic implications**
Blockade of voltage-gated sodium-channels and decreased release of excitatory neurotransmitters such as glutamate.	Continue in the perioperative period. The dissociative effects of ketamine can be decreased.

and neuroleptic malignant syndrome. Many antipsychotics can prolong the QTc interval. This is potentiated with concomitant use of other drugs that prolong QTc intervals, such as ondansetron.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome is rare but potentially life-threatening. Table III summarises the cause, diagnosis, and management.[8]

Table III: Summary of neuroleptic malignant syndrome[8]

Neuroleptic malignant syndrome	
Associated drugs	Typical antipsychotics and antiemetic drugs.
Mechanism of action	Unknown but likely a dopamine receptor blockade leading to parkinsonian-type symptoms.
Symptoms	Classic tetrad: fever, rigidity, mental status change, and autonomic instability.
Diagnosis	Clinical with a history of antipsychotics or other associated medications.
Laboratory tests	Elevated creatine kinase, leucocytosis, low serum iron, hypocalcaemia, and hyperkalaemia.
Management	Stop the offending agents. Supportive care within an intensive care unit. If severe, consider dantrolene, benzodiazepines, bromocriptine, or amantadine.

Conclusion

Optimal perioperative outcomes for patients using neuropsychiatric agents require a good understanding of all the pharmacological classes, as well as the physiological effects of the various treatments. As psychiatry treatments continue to advance, new agents are introduced and explored. It is expected that the anaesthetist is up to date with the various agents and their implications in the perioperative period.

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References

1. Bagwathpersad N. Antidepressant prescribing in Gauteng: a public sector drug utilization review [Internet]. University of the Witwatersrand; 2016. Available from: http://hdl.handle.net/10539/21197. Accessed 11 August 2023.
2. Pryor KO, Storer KP. Drugs for neuropsychiatric disorders. In: Hemmings H, Egan T, editors. Pharmacology and physiology for anesthesia: foundations and clinical application. Elsevier; 2013. https://doi.org/10.1016/B978-1-4377-1679-5.00011-9.
3. Craig A, Rochat T, Naicker SN, et al. The prevalence of probable depression and probable anxiety, and associations with adverse childhood experiences and socio-demographics: a national survey in South Africa. Front Public Health. 2022;10:986531. https://doi.org/10.3389/fpubh.2022.986531.
4. Nguse S, Wassenaar D. Mental health and COVID-19 in South Africa. S Afr J Psychol. 2021;51(2):304-13. https://doi.org/10.1177/00812463211001543.
5. Ho S, Wong A. Perioperative management considerations in patients taking prescribed psychoactive medications (including those for depression and Parkinson's disease). Curr Opin Anaesthesiol. 2021;34(5):582-9. https://doi.org/10.1097/ACO.0000000000001041.
6. Attri JP, Bala N, Chatrath V. Psychiatric patient and anaesthesia. Indian J Anaesth. 2012;56(1):8-13. https://doi.org/10.4103/0019-5049.93337.
7. Moodley A, Kuhn M, Milner A. Central nervous system and neurotransmitters: clinical applications. In: Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. Johannesburg: Milner and Welch (Pty) Ltd; 2019. p. 118-57.
8. Martinez-Baladejo M, Liongson FAZ, Wong D, et al. Anesthetic concerns in psychiatric disease. In: Ng-Pellegrino A, Stawicki SP, editors. Updates in anesthesia: the operating room and beyond. Rijeka: IntechOpen; 2023. https://doi.org/10.5772/intechopen.110173.
9. Hirsch M, Birnbaum RJ. Selective serotonin reuptake inhibitors: pharmacology, administration, and side effects [Internet]. UpToDate; 2022. Available from: https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects?search=Selective%20serotonin%20reuptake%20inhibitors:%20Pharmacology,administration,%20and%20side%20effects&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 20 July 2023.
10. McClure-Begley TD, Roth BL. The promises and perils of psychedelic pharmacology for psychiatry. Nat Rev Drug Discov. 2022;21(6):463-73. https://doi.org/10.1038/s41573-022-00421-7.
11. Scuteri D, Corasaniti MT, Tonin P, Nicotera P, Bagetta G. New trends in pharmacological control of neuropsychiatric symptoms of dementia. Curr Opin Pharmacol. 2021;61:69-76. https://doi.org/10.1016/j.coph.2021.09.002.
12. Mayet S. A review of common psychedelic drugs. S Afr J Anaesth Analg. 2020;26(6):S113-7. https://doi.org/10.36303/SAJAA.2020.26.6.S3.2554.
13. Foster SW. The right to privacy in the decriminalisation of psilocybin mushrooms in South Africa. Law Democr Dev. 2023;27:1-30. https://doi.org/10.17159/2077-4907/2023/ldd.v27.1.
14. Tai C-Y, Liu H-Y, Cata JP, et al. The association between general anesthesia and new postoperative uses of sedative-hypnotics: a nationwide matched cohort study. J Clin Med. 2022;11(12):3360. https://doi.org/10.3390/jcm11123360.

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FCA REFRESHER COURSE

Pharmacology for chemotherapy and immunosuppressants

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Introduction

Cancer is the second leading cause of death globally and accounts for 10% of deaths in South Africa.[1,2] Patients with a history of cancer have shown increased survival with the use of treatment. Anaesthetists frequently encounter patients in all stages of cancer and cancer treatment.[3]

There is a global increase in solid organ transplantation. Increased survival amongst transplant recipients is observed due to improved surgical techniques and immunosuppressive therapy. Patients on immunosuppressive treatment therefore present for transplant and non-transplant related surgery.[4]

The majority of chemotherapy targets cancer cells during rapid division and proliferation. However, the disruption of cell division also affects normal functioning cells in organs involved and uninvolved, resulting in acute/chronic injury after exposure. By understanding the mechanisms of chemotherapy drugs on targeted cancer cells, it is possible to predict what injuries might occur in the rest of the body.[3] Consequently, to understand how chemotherapy interferes with cell division, we must revisit the cell cycle.

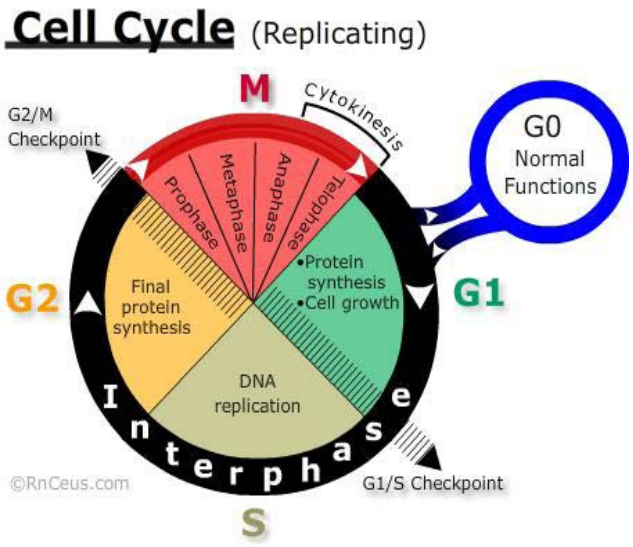

Figure 1: The cell cycle

The cell cycle

The cell cycle is the way cells replicate. It consists of a sequence of cellular events that occur in phases regulated by chemical signals. The eukaryotic cell cycle lasts 24 hours and consists of five phases (Figure 1).[5]

G0/resting stage – Normal metabolic function. Once the cell gets a signal, it starts to replicate.

G1-phase (1st gap) – Involves growth, metabolic activity, and synthesis of ribonucleic acid (RNA).

S-phase – Deoxyribonucleic acid (DNA) synthesis.

G2-phase (2nd gap) – Cell prepares for cell division.

M-phase – Mitosis/cell division occurs.

Proto-oncogenes stimulate cellular growth and division, while tumour suppressor genes restrict the cell cycle progression during G1, before the S-phase.[6] Chemotherapy drugs target cells at different phases of the cell cycle.

Classification of chemotherapeutic agents

Chemotherapeutic agents can be classified based on their mechanism of action (MoA), chemical structure, or relationship to other drugs.[3] Based on the MoA they can be cell-cycle specific (work on specific parts of the cell cycle), cell-cycle nonspecific (effective during all phases of the cell cycle), or hormonal.[6]

Cell-cycle specific

Antimetabolites

Examples: Folate analogue methotrexate (MTX). Purine analogues such as 6-mercaptopurine, azathioprine, and 6-thioguanine. Pyrimidine analogues such as 5-fluorouracil (5-FU), cytarabine, and floxuridine.[3]

MoA: They act as analogues of purine and pyrimidines and inhibit enzymes involved in the cellular metabolism of nucleic acids. They disrupt DNA/RNA synthesis in the S-phase of the cell cycle.[7]

Uses: Treatment of leukaemia, colorectal, bladder, and pancreatic cancers.

Side effects: Immunosuppression, nausea and vomiting, ulcerative stomatitis, diarrhoea, and haemorrhagic enteritis with potential intestinal perforation. MTX causes renal and hepatic toxicity, and pulmonary oedema/effusions, and 5-FU causes myocardial ischemia and acute cerebellar syndrome.[8] Mercaptopurine causes cholestatic jaundice, hyperuricemia, and hyperuricosuria.[7]

DNA synthesis enzyme inhibitors

Examples: Topoisomerase I inhibitors topotecan and irinotecan. Topoisomerase II inhibitors epipodophyllotoxins (e.g. etoposide) and anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin).[3]

MoA: They work by inhibiting the enzyme topoisomerase, which cleaves supercoiled DNA strands so they can be copied during the S-phase of the cell cycle. Inhibiting topoisomerase prevents DNA replication and these agents produce oxygen-free radicals. Topoisomerase I inhibitors prevent supercoiling by cleaving one strand while topoisomerase II inhibitors prevent the cleavage of two strands.[3]

Uses: Topotecan is used in leukaemia, lymphoma, ovarian, cervical, renal, and small-cell lung cancers. Irinotecan is for colorectal cancers.[3] Anthracyclines are mostly used in breast, lung, and bladder cancers as well as leukaemia and lymphomas.[7]

Side effects: Topoisomerase I inhibitors cause severe diarrhoea. Topoisomerase II inhibitors are cardiotoxic (oxygen-free radical production and topoisomerase inhibition in the cardiomyocyte alters calcium-channel activity, and causes arrhythmias, restrictive cardiomyopathy, and congestive heart failure).[3]

Enediynes

Examples: Actinomycin D (dactinomycin) and bleomycin.

MoA: These are antineoplastic antibiotics that damage DNA by oxidation and cleave the DNA strands in the G2-phase of the cell cycle. Dactinomycin disrupts DNA transcription by preventing elongation by RNA polymerase. Bleomycin interacts with iron to produce oxygen-free radicals and is inactivated by the amidohydrolase enzyme (found throughout the body except in the skin and the lungs).[3]

Uses: Treatment of cervical, breast, ovarian, skin, penis, rectal, head, and neck cancers as well as lymphomas.[3]

Side effects: Dactinomycin causes hepatic veno-occlusive disease and clotting disorders. Bleomycin causes painless flagellate hyperpigmentation in the skin and accumulates in the lungs, causing pulmonary fibrosis. Exposure to a high oxygen concentration perioperatively in patients on bleomycin can potentiate bleomycin pneumotoxicity and acute respiratory distress syndrome. The use of supplemental oxygen should be limited to < 30% or used as necessary to keep SaO_2 > 90%.[3]

Microtubule-binding agents

Microtubules provide the basic organisation of the cell's cytoplasm. They are critical in actively dividing cells as they create mitotic spindle, which segregates chromosomes during cellular division. Inhibition of microtubule activity prevents cellular proliferation and suppresses cell migration by vascular endothelial cells, leading to antiangiogenesis, and precluding tumour metastasis. There are two classes of anti-microtubular drugs that function by destabilising or stabilising the microtubules in the cell.[3]

i. Microtubule destabilisers

Examples: Vinca alkaloids such as vinblastine, vincristine, and vinorelbine.

MoA: They bind to the microtubular protein tubulin at the end of the microtubule, terminating the assembly and depolymerisation of the microtubules. This causes the arrest of mitosis in metaphase and chromosomes cannot segregate.[3]

Uses: Lymphomas and leukaemia.

Side effects: Nausea, vomiting, bone marrow suppression, and alopecia. Vincristine is neurotoxic (areflexia, muscle weakness, cranial nerve palsy, especially CN VI, sensory and motor peripheral neuropathy, laryngeal nerve paralysis [10% patients], and syndrome of inappropriate antidiuretic hormone secretion [SIADH]).[7] Vinorelbine causes chest pain, dyspnoea, bronchospasm, and pulmonary infiltrates.[8]

ii. Microtubule stabilisers

Examples: Taxanes such as paclitaxel and docetaxel (synthetic taxane).

MoA: They bind to the beta-tubulin subunit, stabilising the microtubule so depolymerisation is prevented, which arrests the cell in metaphase and halts mitosis.[8] Paclitaxel binds to the B-cell lymphoma 2 (Bcl-2) protein, inducing apoptosis and docetaxel inhibits vascular endothelial growth factor (VEGF) in addition to stabilising the microtubule.[3]

Uses: Testicular cancer, lymphoma, and leukaemia

Side effects: Neurotoxicity.

Cell-cycle nonspecific

They work on all phases of the cell cycle.

Alkylating agents

Examples: Nitrosoureas like carmustine, alkyl sulfonate such as busulfan, nitrogen mustards such as cyclophosphamide, ifosfamide and platinum drugs such as cisplatin.

MoA: Toxic in all phases of the cell cycle but most effective as antiproliferative drugs. The alkyl group covalently binds to DNA at the N7 position of the guanine nucleotide, forming a crosslinking of the DNA. This prevents subsequent transcription and arrests the cell replication in late G1 and S phases.[7] Platinum

drugs do not alkylate DNA but permanently bind to guanine residues in DNA.[3]

Uses: Treatment of Hodgkin's lymphoma, lymphosarcoma, leukaemia, and bronchogenic sarcomas. Platinum drugs are used in testicular, ovarian, bladder, head and neck, and small-cell lung cancer.[3]

Side effects: They have a dose-dependent toxicity usually targeting rapidly growing tissues. They affect the gastrointestinal tract (nausea, vomiting, diarrhoea) and cause bone marrow suppression (leukopenia, anaemia, thrombocytopenia), pulmonary fibrosis (busulfan, nitrosoureas, cyclophosphamide), neuropathies and nephrotoxicity (platinum drugs), and cyclophosphamide causes alopecia, haemorrhagic cystitis, and inhibits plasma pseudocholinesterase (prolonging the effect of suxamethonium).[3]

Antitumour antibiotics

Most of the antineoplastic antibiotics are produced by *Streptomyces* bacteria. They alter the DNA in cancer cells and prevent replication.[6] They are classified based on the mechanism of DNA damage:

a. Alkylate DNA includes adozelesin, bizelesin, and tallimustine.
b. Alkylate produce oxygen radicals, such as mitomycin C and streptonigrin.
c. Topoisomerase inhibitors produce oxygen radicals, and topoisomerase II inhibitors such as anthracyclines (daunorubicin, doxorubicin, epirubicin, and idarubicin).
d. Other antineoplastic antibiotics such as bleomycin and actinomycin D.[9]

Uses: Treatment of leukaemia, lymphoma, breast, and bladder cancers. Mitomycin C is used for squamous cell cancer of the cervix and adenocarcinomas of the stomach, pancreas, and lungs, and topical intravesical treatment of bladder papillomas.[3]

Side effects: Mitomycin C causes renal toxicity and acute pneumonitis leading to pulmonary fibrosis.[8] The rest have been discussed above.

Hormonal agents

Sex hormones and adrenocortical hormones are used in the management of several neoplastic diseases. Steroid hormones work by binding to receptor proteins in cancer cells, forming a steroid-receptor complex that binds directly to the nuclear nonhistone protein of DNA to activate the transcription of the associated cluster of genes. Most steroid-sensitive cancers have specific receptors.[7] Examples of steroid hormone drugs are discussed below.

Adrenocorticosteroids

Glucocorticoids are produced by zona fasciculata and reticularis, and mineralocorticoids are produced by zona glomerulosa. The main endogenous glucocorticoid is hydrocortisone, and the rest are synthetic with relative potencies indicated in Table I below. They have anti-inflammatory, metabolic, and immunosuppressive effects.[10]

Table I: Relative potencies of glucocorticoids[10]

Drug	Relative potencies	Equivalent doses (mg)
Hydrocortisone	1	100
Prednisolone	4	25
Methylprednisolone	5	20
Dexamethasone	25	4

They are used as prophylaxis for transplant rejection, in the treatment of haematological malignancies, autoimmune diseases, and the management of inflammatory and allergic conditions.

Adrenocorticosteroids cause immunosuppression by antiproliferation, and they inhibit T lymphocyte activation by downregulating the expression of cytokines (Interleukin-1, 2 and 6) in macrophages. They reduce plasma antibody levels, decrease capillary permeability, and decrease peripheral lymphocyte counts. Adrenocorticosteroids cause anti-inflammation by inhibiting circulating polymorphs and macrophages from reaching inflamed tissue, hence suppressing the production of inflammatory mediators (prostaglandins and leukotrienes).[10]

Side effects include adrenal suppression, fluid retention, hypertension, diabetes, increased susceptibility to infection, Cushing's syndrome, poor wound healing, bone disease (avascular necrosis and osteopenia), cataracts, muscle wasting, proximal weakness, skin thinning, psychosis, and insomnia.[7,10]

Oestrogens

Fosfestrol and ethinylestradiol are used in oestrogen-sensitive breast and prostate cancer. Side effects include hypercalcaemia and feminisation.[7]

Progestins

Hydroxyprogesterone acetate is used in endometrial, breast, and prostate cancer.

Antioestrogen

Tamoxifen is used in breast and progesterone-resistant endometrial cancer. It functions as a competitive inhibitor of oestrogen, binding to oestrogen-receptor proteins and preventing oestrogen-stimulated increases in oestrogen-sensitive tissues and tumours. It causes hot flushes, deep vein thrombosis, and nausea.[7]

Antiandrogen

Flutamide is used in the treatment of prostate cancer and to antagonise the androgenic effects after orchiectomy. Side effects include feminisation, skeletal muscle weakness, and methemoglobinemia.[7]

5-alpha-reductase inhibitor

Finasteride is used in the treatment of prostate cancer.

Gonadotrophin-releasing hormone agonists

Leuprolide acetate, nafarelin, and goserelin are analogues that inhibit follicle-stimulating hormone and luteinising hormone, causing reduced testicular androgen synthesis. They are used in the treatment of metastatic prostate cancer. Side effects include painful gynaecomastia, nausea, vomiting, oedema, and thromboembolism.[7]

Aromatase inhibitors

Aminoglutethimide (Cytadren) inhibits adrenal steroid synthesis, preventing the conversion of cholesterol to pregnenolone and inhibits the aromatase conversion of adrenal androgen androstenedione to estrone. It is used in treating metastatic breast cancer (oestrogen and progesterone receptor-sensitive). Side effects include dizziness, lethargy, blurred vision, and rash.[7]

Immunosuppressants

These agents play an important role in the prevention and treatment of tissue transplant procedures and the management of certain diseases associated with immunity disorders.[7] Immunosuppressive drugs can be used before transplantation (induction phase), maintenance (long-term drugs), or as anti-rejection therapy. Graft rejection can be hyperacute (< 24 hours), acute (within the first few weeks), or chronic (months to years later).[9] Immunosuppressants are classified according to their mode of action.

Inhibitors of cytokine synthesis

i. Cyclosporine

This is a calcineurin inhibitor. Calcineurin is a protein phosphatase that activates T cells by dephosphorylating a cytoplasmic transcription factor (nuclear factor of activated T cells [NFAT]), which migrates to the nucleus and induces transcription and upregulation of Interleukin-2 (IL-2). IL-2 causes growth and differentiation of T cells. Calcineurin inhibitors blunt signal transduction in T lymphocytes, leading to the suppression of T cell proliferation and response of helper T lymphocytes.[9]

MoA: The calcineurin inhibitor prevents IL-2 T cell proliferation and increases the expression of transforming growth factor (TGF).

Pharmacokinetics: It has 30–90% oral bioavailability, is lipophilic, and has a half-life of 8–27 hours.[11,12]

Uses: Induction and maintenance of immunosuppression in transplant, severe rheumatoid arthritis, and psoriasis.[9]

Side effects: Hypertension, nephrotoxicity (vasoconstriction in the glomerulus leading to renal dysfunction, usually the reason for modifying or stopping the drug), neurotoxicity (tremors, seizures, can prolong the effect of non-depolarising muscle relaxants necessitating a decrease in dose), metabolic problems (hypertriglyceridemia and insulin resistance), gingival hyperplasia (due to increased TGF), and hirsutism. Metabolised by P450, especially CYP3A4, and can have drug interactions with enzyme inducers or inhibitors.[13]

ii. Tacrolimus (FK-506)

MoA: Binds to FK-binding protein 12 (FKBP-12) in the cytoplasm, which interacts and inhibits calcineurin and inhibits the expression of tumour necrosis factor-beta (TNFb). It is highly protein-bound, especially with albumin and alpha-1 glycoprotein, hence close monitoring of blood levels is essential.

Pharmacokinetics: It can be administered orally, sublingual, topical, or intravenously. The half-life is 4–12 hours with a 30 L/kg volume of distribution. It is metabolised by CYP3A4 and about 95% is excreted in bile with 2.4% excreted in the urine unchanged.[12]

Uses: Macrolide antibiotic used for the maintenance of immunosuppression and rescue therapy in acute rejection post-liver transplant.

Side effects: Nephrotoxicity, hypertension, and neurotoxicity (avoid excessive hyperventilation as this can trigger seizures). Drugs inhibiting the CYP3A4 enzyme (like calcium-channel blocker, antifungal, or metoclopramide) or CYP3A4 enzyme inducers, like anticonvulsants, can increase and decrease blood concentrations of tacrolimus respectively.[13]

iii.Sirolimus

MoA: It binds to immunophilin (FKBP-12) in the cytoplasm and the complex inhibits the "target of rapamycin" (mTOR), which is a protein kinase that suppresses the cell division and proliferation of T cells.[13]

Pharmacokinetics: It has rapid gastrointestinal absorption with a peak concentration in one hour (70% of patients) and a half-life of 62 hours.[13] It is hydrophobic and mainly metabolised in the liver, with 92% of metabolites excreted in bile and 1.2% in urine.[12]

Uses: Macrolide antibiotic used as prophylaxis for kidney transplant rejection or in combination with FK-506 and glucocorticoids to decrease their side effects. Also used in drug-eluting stents to prevent endothelial growth over the stent.[9]

Side effects: Pancytopenia, marked hyperlipidaemia (due to inhibition of lipoprotein lipase), and drug interaction with CYP3A enzyme inhibitors/inducers.

iv.Monoclonal anti-CD25 antibodies

Basiliximab (Simulect) and daclizumab (Zenapax) block the IL-2 receptor directly, downregulating the immune system. Daclizumab blocks the CD25 receptor, hence it is used in treating relapsing multiple sclerosis and as an induction immunosuppressive agent. Side effects include anaphylaxis.[8]

Inhibitors of DNA synthesis

i. Mycophenolate mofetil

This is used as a maintenance immunosuppressant and for chronic rejection. It is an ester drug that is hydrolysed to mycophenolic acid (active component), a selective non-competitive inhibitor of inosine monophosphate dehydrogenase (IMPDH), essential for purine synthesis. This causes impaired activity and proliferation of B and T cells.[9] Side effects include pancytopenia, diarrhoea, and vomiting.

ii. Azathioprine

A derivative of 6-mercaptopurine that is subsequently metabolised by xanthine oxidase to 6-thioguanine nucleotides and inhibits purine synthesis. It is used as a maintenance immunosuppressant and autoimmune treatment.[7] It inhibits lymphocyte proliferation and purine synthesis (consequent decreased DNA and RNA synthesis). Side effects include myelosuppression, hepatic dysfunction, pancreatitis, transient antagonism on non-depolarising muscle blockers, and drug interaction with allopurinol (decrease azathioprine dose by one-third to prevent toxicity).[9]

Inhibition of T cell interaction

i. Steroids

Prednisone, dexamethasone, and cortisone are discussed above under adrenocorticosteroids.

ii. Muromonab-CD3 (orthoclone OKT3)

This is a murine monoclonal antibody (mAb) used primarily as induction in patients undergoing a transplant, especially kidney. They bind to the CD3 receptor of T lymphocytes inhibiting its activation. Side effects include pulmonary oedema, anaphylaxis, and cytokine release syndrome (fever, headache, bronchospasm, hypotension, and tachycardia).[9]

Inhibitors of adhesion molecules

i. Antithymocyte globulin (ATG)

This is used as an induction immunosuppressant and in the management of acute rejection in kidney transplants.[9] Antithymocyte globin have cytotoxic antibodies that bind to antigen makers (CD2, CD3, CD4, CD8, CD44, and HLA class I molecules) on the surface of T cells causing the inhibition of T cell function and decreased circulating lymphocytes.[9] Side effects include anaphylaxis, serum sickness, and leukopenia. These are minimised by slow infusion.[9]

Other mAbs

i. TNFa inhibitors

Adalimumab, infliximab, and etanercept are used in haematological malignancies and autoimmune conditions (inflammatory bowel disease, rheumatoid arthritis, psoriasis, and sarcoidosis).[7] mAbs are Fc-fusion proteins inhibiting TNFa. Etanercept is not a mAb but works as a decoy TNFa receptor fusion protein at the Fc portion of immunoglobulin G (IgG).[14] Side effects include the reactivation of latent tuberculosis (must test for tuberculosis before commencing this treatment), heart failure, and neurotoxicity (demyelination).[13]

ii. Rituximab

A chimeric mouse/human IgG1-kappa murine mAb. It is used in the treatment of B cell lymphoma, leukaemia, and autoimmune conditions like rheumatoid arthritis and myasthenia gravis. It binds to CD20 and enhances the destruction of B cells leading to decreased B cell levels. Side effects include anaphylaxis, acute kidney injury, bowel obstruction, tumour lysis syndrome, and pulmonary toxicity.[12]

iii.VEGF inhibitors

Bevacizumab selectively binds VEGF and inhibits VEGF from binding to its receptor, hence inhibiting angiogenesis.[13]

Anaesthetic implication of chemotherapeutic and immunosuppressive agents

There are several challenges when faced with patients on cancer treatment or immunosuppressants, from deranged physiology, tumour-associated effects, toxicity of chemotherapy/immunosuppressants, and drug interactions.[15] Various anaesthetic agents interact with chemotherapy and immunosuppressants differently.

Volatile anaesthetics

Volatiles have positive and negative effects when combined with chemotherapeutic agents. Halothane enhances the antitumour effect of IFN-γ when combined in patients with colon cancer. Sevoflurane suppresses cell growth in combination with cisplatin for the management of adenocarcinoma in the lungs but causes chemoresistance in renal cell cancer. Isoflurane causes chemoresistance in prostate cancer while sevoflurane enhances cancer progression in breast cancer.[15]

Intravenous drugs

Propofol enhances the effect of chemotherapy in ovarian and pancreatic cancer but decreases the cytotoxicity of cisplatin when used together. Ketamine causes apoptosis and decreased proliferation in ovarian, gastric, and pancreatic cancer.[15] Anthracycline-based chemotherapeutic agents and mAb agents, like trastuzumab, cause significant cardiotoxicity. In combination with anaesthetics that prolong the QT interval, like halothane, propofol, or beta-2 agonists, it leads to fatal arrhythmias. Renal toxicity of calcineurin inhibitors can have significant interactions with anaesthetic agents and fluid management.

Opioids

Morphine, in particular, decreases the cytotoxic effects of chemotherapeutic agents and causes immunosuppression. Morphine also causes angiogenesis, increased prostaglandins, increased expression of mu receptors and is a natural killer of cell expression in breast and lung cancer, hence it can increase the risk of cancer recurrence.[3] Alpha-2 agonists and nonsteroidal

anti-inflammatory drugs (NSAIDs) have beneficial effects on pain management in cancer patients.

Regional anaesthetics

These have antitumour effects and increase the efficacy of chemotherapy agents when given together. Local anaesthetics, especially lidocaine, have been shown to sensitise tumours to chemotherapy.

Oxygen

Hypoxia causes resistance to radiotherapy and chemotherapy since oxygen is important for DNA damage. However, perioperative use of high concentrations of oxygen in patients on certain medications, like bleomycin, can potentiate bleomycin pneumotoxicity and acute respiratory distress.

Conclusion

Anaesthetics, stress, pain, hypothermia, hyperglycaemia, and other factors that anaesthesiologists encounter are immunomodulators and play a role in increasing or decreasing cancer recurrence. Conducting good clinical history and examination as well as excluding metabolic derangements in patients coming to theatre for surgery on chemotherapy or immunosuppressive drugs is essential. Patients should continue immunosuppressants perioperatively. Meticulous infection control is essential as these patients are prone to infections. Good knowledge of side effects and drug interactions impacts the type of anaesthesia administered and should be known by all anaesthesiologists.

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References

1. Finestone E, Wishnia J. Estimating the burden of cancer in South Africa. S Afr J Oncol. 2022;6:1-7. https://doi.org/10.4102/sajo.v6i0.220.
2. Statssa.gov.za [Internet]. Mortality and causes of death in South Africa: findings from dead notification. South Africa: Department of Statistics; 2018. p. 1-149. Report No.: P0309.3. Available from: http://www.statssa.gov.za/publications/P03093/P030932018.pdf. Accessed 16 August 2023.
3. Hemmings HC, Egan TD, editors. Pharmacology and physiology for anesthesia: foundations and clinical application. 2nd ed. Philadelphia: Elsevier; 2019.
4. Brusich KT, Acan I. Anesthetic considerations in transplant recipients for nontransplant surgery [Internet]. In: Tsoulfas G, editor. Organ donation and transplantation - current status and future challenges. IntechOpen; 2018. https://doi.org/10.5772/intechopen.74329.
5. Cooper GM. The eukaryotic cell cycle [Internet]. Sunderland: Sinauer Associates; 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK9876/. Accessed 31 August 2023.
6. Mustapha A, Ismail A, Abdullahi S, et al. Cancer chemotherapy: a review update of the mechanisms of actions, prospects and associated problems. J Biomed. 2022;01(01):001-16. https://doi.org/10.53858/bnas01010119.
7. Katzung BG. Basic and clinical pharmacology. 5th ed. Norwalk (Conn.): Appleton & Lange; 1992.
8. Milner A, Welch E, editors. Applied pharmacology in anaesthesiology and critical care. 2nd ed. Milner and Welch (PTY) LTD; 2019.
9. Freeman BS, Berger JS, editors. Anesthesiology core review: part 1, basic exam. New York: McGraw-Hill Education Medical; 2014.
10. Peck T, Harris B. Pharmacology for anaesthesia and intensive care. 5th ed. Cambridge University Press; 2021. https://doi.org/10.1017/9781108591317.
11. Liu L, Ren B, Zhang H, et al. Population pharmacokinetic analysis of mizoribine in Chinese renal transplant recipients. Transplant Proc. 2018;50(8):2392-7. https://doi.org/10.1016/j.transproceed.2018.03.030.
12. Hussain Y, Khan H. Immunosuppressive drugs. Encycl Infect Immun. 2022;4:726-40. https://doi.org/10.1016/B978-0-12-818731-9.00068-9.
13. Marczin N, Racz K. Antirejection drugs and immunosuppressants [Internet]. In: Evers AS, Maze M, Kharasch ED, editors. Anesthetic pharmacology. 2nd ed. Cambridge University Press; 2013. p. 830-41. https://doi.org/10.1017/CBO9780511781933.053.
14. Dörner T, Kay J. Biosimilars in rheumatology: current perspectives and lessons learnt. Nat Rev Rheumatol. 2015;11(12):713-24. https://doi.org/10.1038/nrrheum.2015.110.
15. Watson J, Ninh MK, Ashford S, et al. Anesthesia medications and interaction with chemotherapeutic agents. Oncol Ther. 2021;9(1):121-38. https://doi.org/10.1007/s40487-021-00149-1.

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FCA REFRESHER COURSE

The physics of altitude and anaesthesia

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As altitude increases there is a reduction in barometric pressure. Gases such as oxygen (O_2) and nitrous oxide (N_2O) have a lower partial pressure and a decreased clinical effect. The partial pressure of volatiles and the performance of vaporisers remain the same at increased altitudes, except for desflurane. Because the density of gas decreases at higher altitudes, equipment such as flowmeters and gas mixing devices function differently.

Keywords: altitude, physics, anaesthesia

Introduction

South Africa's major cities are located at various altitudes. High altitude is defined as an elevation greater than 1 500 m, which includes most of Gauteng.[1] Globally, about 140 million people live above 2 500 m and an equal number will visit high altitudes each year.[2] Consequently, anaesthetists require an understanding of how respiratory and anaesthetic gases behave under conditions of altered barometric pressure.[3] As altitude increases and barometric pressure falls, the partial pressure and density of gases decrease. There must be an awareness of the potential for hypoxia, decreased anaesthetic effectiveness, equipment recalibration, and the accuracy of certain equipment at altitude.

Gases

Oxygen

The partial pressure of oxygen (PO_2) remains at 21% of barometric pressure regardless of altitude. As altitude increases, barometric pressure decreases by approximately 70 mmHg per 1 000 m above sea level (Figure 1). This equates to a PO_2 of 160 mmHg at sea level and 134 mmHg in Johannesburg. Saturated vapour pressure (SVP) is temperature dependent and so remains 47 mmHg at any altitude. Table I shows the fall of inspired partial pressures of oxygen as altitude increases.

To avoid vulnerability to hypoxia during routine anaesthesia (shunting, V/Q mismatching, and hypoventilation), it has been recommended that patients with normal lung function should be administered a minimum inspired partial pressure of oxygen ($PinspO_2$) of 215 mmHg.[4] For the anaesthetist, this would mean dialling a minimum fraction of inspired oxygen (FiO_2) of 30% at sea level, 35% in Johannesburg (1 700 m), 40% at 3 000 m, and 100% on Mount Everest.

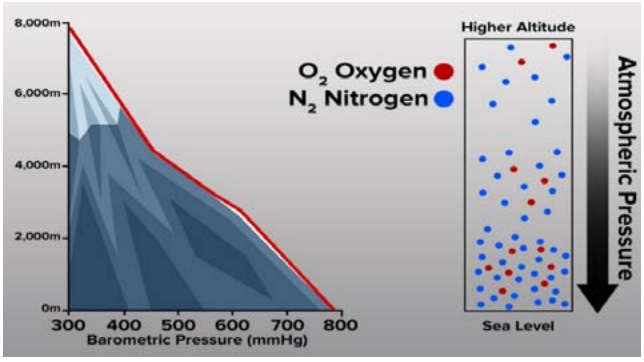

Figure 1: Fall in barometric pressure as altitude increases

Nitrous oxide

Like oxygen, N_2O is a gas at room temperature and its clinical effectiveness is dependent on its partial pressure. Because partial pressure drops with barometric pressure, N_2O's analgesic potency decreases with altitude. In his study on the analgesic effect of 50% N_2O in O_2, James et al.[5] showed that analgesic effectiveness decreased from 70% at sea level to 40% at 1 600 m, to just 19% at 3 000 m. At very high altitudes, its lack of clinical effect and the risk of hypoxia with its use in an already oxygen-depleted environment have condemned its use.[6]

Table I: Knowing your O_2 at altitude; O_2 cascade at increasing altitudes

	Sea level	Johannesburg (1 700 m)	Mount Everest (8 848 m)
P atm	760 mmHg	640 mmHg	253 mmHg
P $atmO_2$	21% × 760 = 160 mmHg	21% × 640 = 134 mmHg	21% × 253 = 53 mmHg
P $inspO_2$	21% × (760 - 47) = 150 mmHg	21% × (640 - 47) = 124 mmHg	21% × (253 - 47) = 43 mmHg
P $AlvO_2$	150 - (40 / 0.8) = 99 mmHg	124 - (35 / 0.8) = 80 mmHg	43 - (13 / 0.8) = 27 mmHg
P $artO_2$	99 - 7 = 92 mmHg	80 - 3 = 77 mmHg	27 - 1 = 26 mmHg

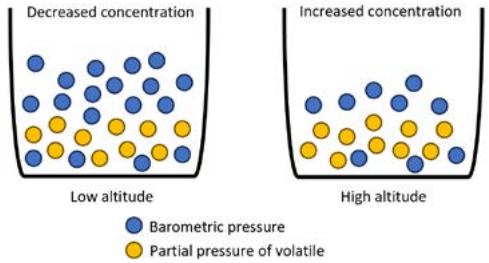

Figure 2: Effect of altitude on a volatile's measured concentration

Volatiles and vaporisers

Volatile potency is determined by the partial pressure of the vapour, also known as its SVP. Since SVP is dependent on temperature and not altitude, the partial pressure of a vapour remains constant at different altitudes. Experiments done at different altitudes with halothane vaporisers showed that, at any given setting, the output and potency remain the same; however, its measured concentration increases as barometric pressure falls (Figure 2).[7]

Desflurane

Desflurane has a high vapour pressure and boiling point near room temperature, making the output concentration delivered by a variable bypass vaporiser unpredictable. The Tec 6 vaporiser (Datex-Ohmeda) heats desflurane to 39 °C, which maintains a vapour pressure of 2 atmosphere (atm) and enables a constant, predictable output concentration of a volatile that behaves more like a pressurised gas. As ambient pressure decreases and output volume concentration remains unchanged, the partial pressure of the anaesthetic will drop. Therefore, to achieve the same potency with desflurane at altitude, the following calibration formula must be used: required dial setting (%) = desired % × (760 mmHg / local barometric pressure in mmHg).[8]

Gas analysers

Oxygen

Measurement of oxygen content in a gas mixture can be done by paramagnetic analysis, a Clark electrode, a fuel cell, or mass spectrometry. All these devices measure partial pressure and convert it to concentration (percentage). They must therefore be recalibrated at altitude. For example, if an oxygen analyser at sea level was not recalibrated in Johannesburg (1 700 m), it would read 17% (134 / 760 mmHg) instead of 21% (134 / 640 mmHg).[9]

Carbon dioxide (CO_2)

Carbon dioxide is measured by the absorption of infrared radiation by the gas and responds to its partial pressure. Fortunately, most analysers today display the output in pressure units (measured at end-expiration as the end-tidal CO_2) and not as a percentage. If percentage is used, the equipment must be recalibrated against known concentrations of CO_2 at the correct barometric pressure.[7]

Vapour analysers

Vapour analysers respond to partial pressure but are invariably calibrated in percentages. As discussed earlier, the concentration of a volatile increases as ambient pressure drops, although the partial pressure remains the same for a given dialled output setting. As a result, these analysers need recalibration at altitude to accurately show the true concentration, which is expected to be higher. Since minimum alveolar concentration (MAC) is a clinical depth of anaesthesia observed and defined at sea level, its concept is not accurate at altitude as higher concentrations are needed to maintain the same partial pressure.[7] Ideally, since partial pressure determines the clinical effect, it is minimal alveolar partial pressure (MAPP) that should be used to define MAC at altitude.[7] There should be an awareness of the increase in measured concentration of volatile required to achieve its MAPP at higher altitudes. Table II shows these concentrations for sevoflurane.[3] The MAC value conversion on most modern-day machines should be accurate if the analyser has been recalibrated at altitude.

Gas flow

Flowmeters

At low flow rates, a flowmeter device acts as a tube and so the flow of gas through it is primarily laminar. Laminar flow is dependent on viscosity, which changes with temperature but not atmospheric pressure. Therefore, at flows less than 3 L/min, provided the temperature is constant, the percentage error of the reading of these devices at altitude is insignificant.[7] At higher flow rates, the bobbin moves up the tapered tube and the resistance behaves more like an orifice that creates turbulence.

Turbulent flow is inversely proportional to the density of the gas, which drops with altitude. James et al.[7] found that at flow rates greater than 3 L/min, the percentage error of the flowmeter reading becomes significant as altitude increases. The actual flow of gas will be greater than indicated by the position of the bobbin. It is suggested that an O_2 analyser should be used when using O_2/N_2O at altitude if O_2 is used at 2 L/min and N_2O at 4 L/min, as the concentration of O_2 could be less than the safe margin of 33% as the flow of N_2O may be greater than 4 L/min with an accurate O_2 of 2 L/min.[9]

Table II: Equivalent values of MAC and MAPP of sevoflurane at various altitudes[3]

	MAC (%)			MAPP	
Agent	Sea level	5 000 ft (1 524 m)	10 000 ft (3 048 m)	(kPa)	(mmHg)
Sevoflurane	2.0	2.4	3.2	2.12	15.9

Venturi masks

These gas mixing devices tend to deliver higher concentrations of O_2 at altitude. The lower ambient pressure results in a lower pressure drop across the inlet orifice, which means less room air is entrained. The resultant gas mixture is therefore richer in oxygen. A venturi mask designed to deliver 35% O_2 at sea level will deliver 41% at 10 000 ft (3 048 m).[2]

Peak flow meters

These devices tend to underestimate peak expiratory flow by 6–8% for every 100 mmHg drop in barometric pressure.[10]

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References

1. Dietz TE. An altitude tutorial [Internet]. International Society for Mountain Medicine; 2011. Available from: https://themountainschool.com/wp-content/uploads/2017/11/Hi-Altitude_tutorial.htm. Accessed 20 July 2023.
2. Miller RD. Miller's anesthesia. 7th ed. Philadelphia: Elsevier; 2010. p. 2502-7.
3. James MFM. Altitude and anaesthesia: part 1 anaesthesia refresher course. University of Cape Town; 2017. p. 30.1-8.
4. Aldrete JA, Romo-Salas F. Oxygenation with high, intermediate and low gas flows during thoracic and abdominal surgery: studies at an altitude of one mile. New York: Grune & Stratton; 1979. p. 53.
5. James MFM, Manson EDM, Dennett JE. Nitrous oxide analgesia and altitude. Anaesthesia. 1982;37(3):285-8. https://doi.org/10.1111/j.1365-2044.1982.tb01100.x.
6. Safar P, Tenicela R. High altitude physiology in relation to anesthesia and inhalation therapy. Anesthesiology. 1964;25:515-31. https://doi.org/10.1097/00000542-196407000-00014.
7. James MFM, White JF. Anesthetic considerations at moderate altitude. Anesth Analg. 1984;63(12):1097-105. https://doi.org/10.1213/00000539-198412000-00008.
8. OpenAnesthesia. Inhaled anesthetics in clinical use. OpenAnesthesia [updated 2023 April 26]. Available from: https://www.openanesthesia.org/keywords/inhaled-anesthetics-in-clinical-use/. Accessed 21 July 2023.
9. Welch E. Altitude and anaesthesia: part 1 anaesthesia refresher course. University of Cape Town; 2009. p. 29.1-5.
10. Jensen RL, Crapo RO, Berlin SL. Effect of altitude on hand-held peak flowmeters. Chest. 1996;109(2):475-9. https://doi.org/10.1378/chest.109.2.475.

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FCA REFRESHER COURSE

Antiemetic agents

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Introduction

Emesis is defined as the forcible emptying of gastric and/or intestinal contents.[1] Nausea and vomiting have many causes, including drugs (nitrous oxide, chemotherapeutic agents, opioids, etc.), radiation therapy, pregnancy, motion sickness, postoperative, pain, etc.[2] Postoperative nausea and vomiting (PONV) occur immediately in the recovery area or up to 24 hours postoperatively.[2] The incidence varies between 30% and 80%, especially if no prophylaxis is given.[2,3]

PONV ranks high on the list of postoperative patient concerns.[2] It can result in wound dehiscence, aspiration, oesophageal rupture, dehydration, raised intracranial pressure, and pneumothorax due to the high pressures generated while retching.[2] The morbidity surrounding PONV itself is enough for anaesthesia to prevent its occurrence (prevention is better than cure). To adequately prevent and treat nausea and vomiting, it is essential to know the pathophysiology, receptors, and signalling molecules.

Definitions

These definitions are described within the realm of chemotherapy-induced nausea and vomiting (CINV) and are not always relevant to the anaesthetist.

Acute - nausea and vomiting within 24 hours of chemotherapy. PONV can be considered an acute form of nausea and vomiting as it is also defined within 24 hours.[1]

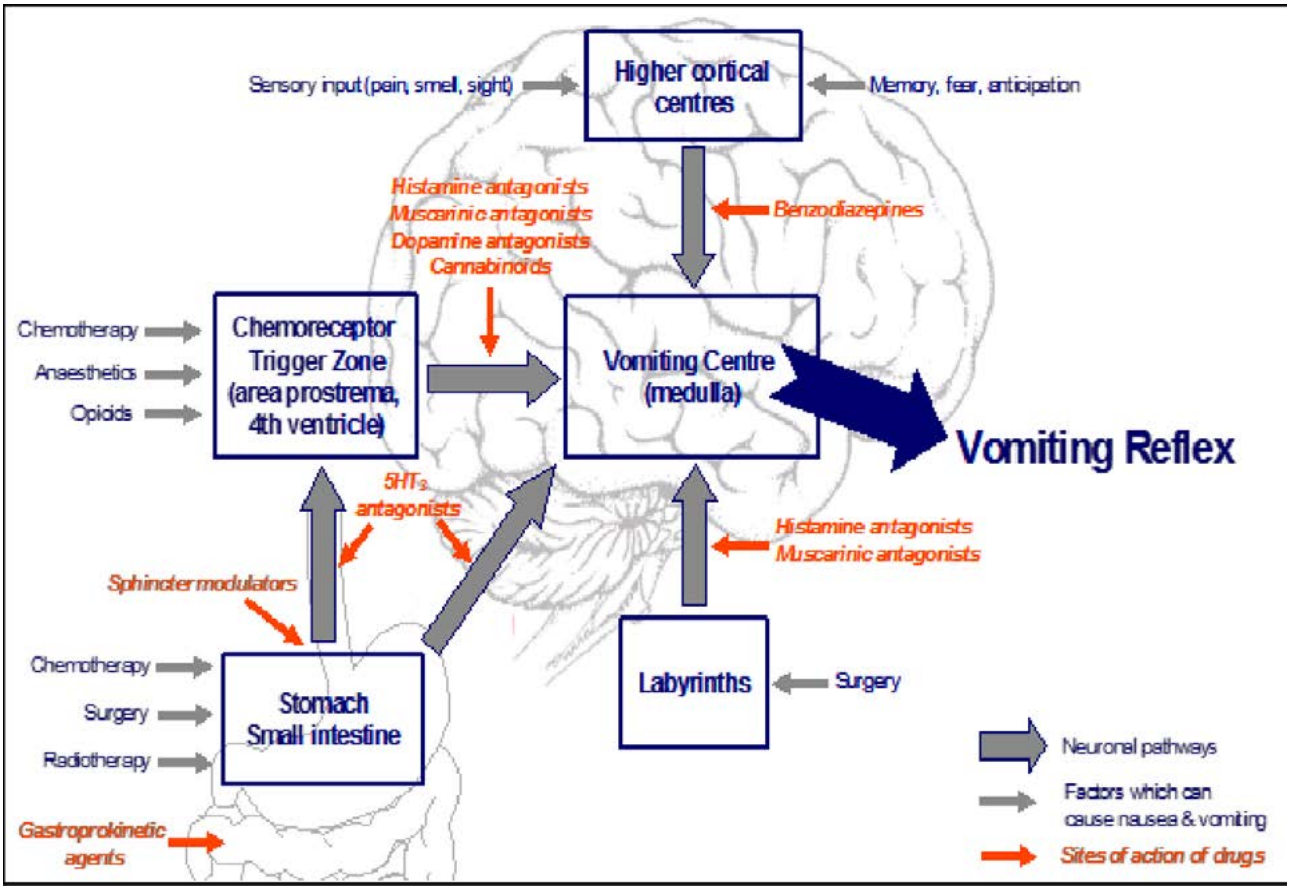

Figure 1: Pathophysiology of emesis[1]

Delayed - nausea and vomiting occurring 24 hours after chemotherapy administration.[1]

Anticipatory - this can be described as a conditioned response and can occur at any point before, during, and after chemotherapy is given. External stimuli can contribute to this type of nausea and vomiting. Anxiety-induced nausea and vomiting can be included in this definition.[1]

Breakthrough - nausea and vomiting that occurs during subsequent cycles of treatment despite prophylactic treatment and requires rescue antiemetics.[1]

Refractory - nausea and vomiting that occurs despite prophylactic and rescue antiemetics being administered.[1]

Postdischarge nausea and vomiting (PDNV) - nausea and vomiting that occurs after discharge for outpatient procedures; it can be acute or delayed in nature.[2]

Pathophysiology

Figure 1 shows the interaction of the various triggers, where they act, as well as the receptors involved in the process. This section should be revised before revising the relevant drugs to improve understanding.

The five receptors directly involved in emesis are muscarinic (M1), histamine (H1), dopamine (D2), serotonin (5-HT3), and neurokinin-1 (NK-1) receptors.[1,2]

Risk factors for PONV

Patient risk factors[2,4,5]

- Preoperative nausea and vomiting
- Female gender
- History of PONV or motion sickness
- Non-smoker
- Age
- CINV

Anaesthesia-related risk factors[2,4,5]

- Anaesthetic technique (general vs. regional)
- Volatile agents versus total intravenous anaesthesia (TIVA)
- Intravenous (IV) anaesthetics
- Nitrous oxide (N_2O) use
- Duration of anaesthesia
- Opioid use
- Neostigmine versus sugammadex for reversal
- Type of surgery: gynaecology, urology, cholecystectomy, laparoscopic procedures, strabismus repair, ear, nose, and throat procedures especially on the inner ear (tympanoplasty and adenotonsillectomy)
- Hydration status

Scoring systems

There are numerous scoring systems, but one of the more commonly used systems is the Apfel Simplified Risk Score for PONV.[5] It is used in adults and only constitutes four factors:[2,5]

1. Female gender
2. Non-smoker
3. History of PONV or motion sickness
4. Expected use of opioids intraoperatively

The presence of 0, 1, 2, 3, and 4 factors correspond to a risk for PONV of 10%, 20%, 40%, 60%, and 80%. Patients are classified into low, medium, or high risk depending on the number of factors present.[5]

Children are more difficult to assess and thus are only assessed for postoperative vomiting (POV).[2] A simplified scoring system by Eberhart et al.[6] is used, which is similar to the Apfel Score:

1. Surgery lasting ≥ 30 minutes
2. Age ≥ 3 years
3. Strabismus surgery
4. History of POV or family history of PONV

A score of 0, 1, 2, 3, and 4 positive factors correspond to a risk of POV of 10%, 10%, 30%, 50%, and 70%.[5,6] Like the Apfel scoring system for adults, risk categories are divided by the number of positive factors.[5]

Non-pharmacological methods to manage PONV[2]

- Acupuncture - P6 point
- Isopropyl alcohol

Pharmacological classification of antiemetics

There are five main classes of drugs, and these are based on the receptors involved in nausea and vomiting and their binding ligands.[2,4,5,7] Table I summarises the various agents that are currently available.

1. M1 receptor antagonists
2. H1 receptor antagonists
3. D2 receptor antagonists
4. 5-HT3 receptor antagonists
5. NK-1 receptor antagonists
6. Adjuvants

M1 receptor antagonists

These agents primarily antagonise the M1 receptors. These drugs are mainly used in the management of nausea and vomiting caused by motion sickness.[1] The most common drug is scopolamine, also known as hyoscine hydrobromide. This drug should not be confused with hyoscine butylbromide (Buscopan), which we commonly see in our theatre drug drawers for IV use. Cyclizine has antagonistic effects on both M1 and H1 receptors and is used for motion sickness. Cinnarizine is indicated for

motion sickness and inner ear diseases causing nausea and vomiting.[1]

H1 receptor antagonists

These drugs are H1 receptor blockers.[1,2] They act centrally and are mainly used as antiemetic agents for motion sickness.[7,8] They are not given routinely as agents for PONV but can be prescribed to offset the extrapyramidal side effect of metoclopramide while complementing its antiemetic effect.[2,9] Examples of drugs within this class are diphenhydramine, dimenhydrinate, and meclizine. Promethazine has antihistamine effects and is sometimes also classified under this group. Common side effects include sedation, dizziness, confusion, dry mouth, and urinary retention.[8,9]

D2 receptor antagonists

Centrally positioned D2 receptors are blocked by this class.[1] There are three divisions of antiemetic drugs within this class, namely phenothiazines, butyrophenones, and benzamides.[4,7]

Prochlorperazine, promethazine, and chlorpromazine fall under phenothiazines and are mainly used for allergies (H1 receptor antagonist), but can be used to treat PONV. Their main side effect is excessive sedation. Less commonly occurring side effects are extrapyramidal effects (dystonia, tardive dyskinesia), hypotension, jaundice, and agranulocytosis. Chlorpromazine is mainly used for motion sickness, after failing to manage symptoms with M1 or H1 receptor blockers.[1,4,7]

Butyrophenones include droperidol, haloperidol, and amisulpride. These drugs potentiate the effects of opioids and tranquillisers.[2] Major side effects are like those for the phenothiazines, but also include a dose dependent interval prolongation on an electrocardiogram (ECG) that can present as QTc prolongation or torsades de pointes.[4,7,8] Droperidol has fallen out of favour due to the QTc prolongation and easy availability of other drugs.

Metoclopramide and domperidone are examples of benzamides. They both have multiple sites of action, both peripherally and centrally. Metoclopramide acts on M1 and 5-HT4 receptors peripherally and on D2 and 5-HT3 receptors centrally.[1,4,8] Domperidone does not cross the blood-brain barrier (BBB), it acts on the chemoreceptor trigger zone (CTZ) by inhibiting D2 receptors and peripherally by inhibiting M1 receptors.[1,7] Side effects are similar to the phenothiazines.[4,8] It is important to note that domperidone cannot cause extrapyramidal effects as it does not cross the BBB.

5-HT3 receptor antagonists

These agents block 5-HT3 receptors both peripherally and centrally. Peripherally, they block 5-HT3 receptors in the gastrointestinal tract (GIT) at vagal nerve terminals. Centrally, they block 5-HT3 receptors within the CTZ.[1] Ondansetron and granisetron are the commonly known agents within this class. Other agents include dolasetron and tropisetron. The most recent additions are the second-generation drugs, palonosetron and ramosetron. Both are long-acting (3–5 days duration of action) and have a higher affinity for the 5-HT3 receptor than first-generation drugs. A single dose of either is sufficient for PONV.[2,7]

Common side effects with this class include headache, dry mouth, fever, malaise/fatigue, and constipation.[7,8] Serotonin syndrome has also been reported as a complication with this class of drugs, but it mainly occurs when used concomitantly with other serotonergic drugs.[7,8,10]

ECG interval prolongation is another serious complication associated with high morbidity.[10] The most well-described example is QTc prolongation associated with ondansetron.[10,11] Other arrhythmias have also been reported; these are usually dose dependent, occurring after IV use and happen more frequently when there is concomitant use of other interval-prolonging drugs.[11]

NK-1 receptor antagonists

This class is unique for having anxiolytic, antidepressant, and antiemetic effects.[12] These drugs cross the BBB and their antiemetic effects are due to substance P regulation via inhibition of NK-1 receptors centrally.[1] Examples include aprepitant, fosaprepitant, rolapitant, and netupitant. This class is best suited for use in delayed onset nausea and vomiting. Common side effects include sleepiness, GIT disturbances, fever, and itching.[2,8,12] More serious side effects include hives/rash and Steven-Johnson syndrome.[7,8,12] Many potential drug interactions can occur with concomitant use, therefore taking a thorough history of medications the patient is currently using is of utmost importance.

Adjuvants

Corticosteroids

Dexamethasone is the most researched drug among the corticosteroids. The mechanism of action is not well understood. Possible mechanisms are:[1,2,4,7,8]

- Changes in the BBB changing permeability to emetogenic substances
- Decreasing brainstem encephalin release
- Inhibiting central prostaglandin synthesis
- Decreasing serotonin synthesis and release
- Depletes gamma-aminobutyric acid (GABA) stores

Only minor side effects have been reported with short-term use, including insomnia and mood changes.[2,4,7,8] Studies have shown that single doses of dexamethasone do not increase surgical site infection rates or result in prolonged raised glucose levels.[2]

Table I: Antiemetic drugs and dosages[2,4,5]

Drug	Dosing
Anticholinergic agents (M1)	
Scopolamine	Transdermal patch applied either the evening before (or at least 4 hours before) surgery or after surgery; 1 patch (1 mg) replaced every 72 hours
Cyclizine (Valoid)	50 mg IV at end of surgery 50 mg p.o. 8 hourly
Histamine receptor antagonists (H1)	
Diphenhydramine (Benadryl)	25–50 mg p.o. 6 hourly 10–50 mg IV 6 hourly (max 400 mg/day) 10–50 mg, up to 100 mg if needed intramuscular (IM) 6 hourly
Dimenhydrinate	1 mg IV at induction 50 mg p.o. 4 hourly
Meclizine	25 mg p.o. 6 hourly
Dopamine receptor antagonists (D2)	
Phenothiazines	
• Prochlorperazine (Stemetil)	5–10 mg IV/IM at end of surgery
• Promethazine (Phenergan)	6.25–12.5 mg IV at induction
Butyrophenones	
• Droperidol (Inapsine)	0.625–1.25 mg IV at induction
• Haloperidol	1 mg IV/IM at end of surgery
• Amisulpride	5 mg IV at induction over 1–2 minutes
Benzamides	
• Metoclopramide (Maxolon)	10 mg IV at induction
• Domperidone	
Serotonin receptor antagonists (5-HT3)	
Ondansetron (Zofran)	4 mg IV at end of surgery 8 mg p.o. 1 hour before induction, then 8 hourly
Granisetron (Kytril)	0.35–3 mg IV at end of surgery, then 12 hourly
Palonosetron (Onicit)	0.075 mg IV as a single dose just before induction
Neurokinin-1 receptor antagonists (NK-1)	
Aprepitant	40 mg p.o. preoperatively; 32 mg IV over 30 seconds preoperatively
Fosaprepitant	150 mg IV preoperatively
Rolapitant	90 mg p.o. preoperatively
Adjuvants	
Corticosteroids	
• Dexamethasone (Decadron)	4–8 mg IV at induction
Cannabinoids	
• Nabilone	1–2 mg p.o. 6–8 hourly
• Dronabinol	5–10 mg p.o. 12 hourly

Cannabinoids

These drugs are currently not indicated for PONV but are included for completeness. The antiemetic effects are via central CB1 and CB2 receptor inhibition.[1] Currently, available drugs are oral nabilone and dronabinol; there are no IV formulations available. They are currently approved for use related to CINV.[1,2,13] Common side effects include vertigo, hypotension, dysphoria, xerostomia, and sedation.[1,13]

Other

Other drugs such as propofol, midazolam, and olanzapine have been used for PONV. Propofol at induction, TIVA maintenance, and sub-hypnotic doses have been shown to have antiemetic effects.[2] Midazolam has been used to prevent anticipatory nausea and vomiting in patients receiving chemotherapy or radiotherapy. Midazolam has no antiemetic effect but causes sedation, which can blunt physiological responses.[2] Olanzapine is a second-generation antipsychotic agent with antiemetic properties via D2 and 5-HT2 receptors. It has highly sedating properties and should be used with caution.[2]

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References

1. Kumar A, Kumar A. Antiemetics: a review. Int J Pharm Sci Res. 2013;4(1):113-23. https://doi.org/10.13040/IJPSR.0975-8232.4(1).13-23.
2. Feinlib J, Kwan LH, Yamani A. Postoperative nausea and vomiting [Internet]. UpToDate; 2023. Available from: https://www.uptodate.com/contents/postoperative-nausea-and-vomiting?search=postoperative%20nausea%20and%20vomiting&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 21 August 2023.
3. Weibel S, Rücker G, Eberhart LH, et al. Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: a network meta-analysis. Cochrane Database Syst Rev. 2020;10(10):CD012859. https://doi.org/10.1002/14651858.CD012859.pub2.
4. Manchester AK, Gan TJ. Antiemetics [Internet]. In: Johnson KB, editor. Clinical pharmacology for anesthesiology. New York: McGraw-Hill Education; 2015. p. 1-9. Available from: https://accessanesthesiology.mhmedical.com/content.aspx?aid=1103964128. Accessed 12 August 2023.
5. Gan TJ, Belani KG, Bergese S, et al. Fourth consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg. 2020;131(2):411-48. https://doi.org/10.1213/ANE.0000000000004833.
6. Eberhart LHJ, Geldner G, Kranke P, et al. The development and validation of a risk score to predict the probability of postoperative vomiting in pediatric patients. Anesth Analg. 2004;99(6):1630-7. https://doi.org/10.1213/01.ANE.0000135639.57715.6C.
7. Longstreth GF, Hesketh PJ. Characteristics of antiemetic drugs [Internet]. UpToDate; 2023. Available from: https://www.uptodate.com/contents/characteristics-of-antiemetic-drugs?search=characteristics%20of%20antiemetic%20drugs&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#references. Accessed 1 September 2023.
8. Hauser JM, Azzam JS, Kasi A. Antiemetic medications [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2022 September 26]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK532303. Accessed 1 September 2023.
9. Schaefer TS, Zito PM. Antiemetic histamine H1 receptor blockers [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 March 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK533003/. Accessed 1 September 2023.
10. Theriot J, Wermuth HR, Ashurst JV. Antiemetic serotonin 5-HT3 receptor blockers [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2022 November 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513318/. Accessed 31 August 2023.
11. Griddine A, Bush JS. Ondansetron [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 February 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499839/. Accessed 31 August 2023.
12. Ibrahim MA, Preuss CV. Antiemetic neurokinin-1 receptor blockers [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 March 24]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470394/. Accessed 1 September 2023.
13. Ibrahim NAM, Mansour YSE, Sulieman AAM. Antiemetic medications: agents, current research, and future directions. Int J Phram Pharm Sci. 2019;4(3):07-14. https://doi.org/10.5281/zenodo.3243134.