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Management of vasoplegia

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Vasoplegia and vasoplegic syndrome (VS) are common sequelae of the inflammatory system following sepsis, anaphylaxis, intoxication, pancreatitis, different states of shock and procedures such as cardiopulmonary bypass (CPB). During CPB, 5–25% of patients may have this complication. It presents with decreased systemic vascular resistance, high cardiac output, increased fluid demand, all symptoms often intractable. This apparent paralysis of the vascular system is a result of activation of vasodilator mechanisms coupled with resistance to innate and exogenous vasoconstrictor mechanisms. Predominantly, the is overactivity of nitric oxide (NO) and deficiency of vasopressin.[1]

Keywords: vasoplegia, vasoplegic syndrome

Cellular mechanism

Calcium plays a major role in the downstream effect of vasoconstriction via voltage-gated channels. Nitric oxide (NO) activates the ATP-sensitive potassium channel (KATP). Other compounds, including atrial natriuretic peptide and adenosine, are important in activation of KATP. Presumably, this is an important physiological mechanism to counteract periods of temporary local tissue ischaemia. On the other hand, vasopressin reduces NO synthesis by directly inactivating KATP channels through binding to arginine vasopressin receptor 1 (AVPR1) receptors.[2]

Risk factors

Several risk factors and underlying mechanisms are largely related to conditions that elicit an inflammatory response. Chronic inflammatory conditions and disease states such as sepsis, adrenal insufficiency, hepatic failure, haemodialysis, haemorrhagic shock, cardiac failure and cardiac surgery are reported to predispose patients to vasoplegic syndrome (VS).[3,4] Acute conditions that lead to broad-based immunological response are driven by a response to ischaemia-reperfusion, endotoxaemia, increased production of oxygen free radicals, and cytokine release.

In cardiac surgery, the additive euroSCORE, procedure type, pre-bypass mean arterial pressure, length of bypass, administration of pre-cardiopulmonary bypass (CPB) vasopressors, core temperature on CPB, pre- and post-CPB haematocrit, the preoperative use of beta-blockers or angiotensin-converting enzyme (ACE) inhibitors, and the intraoperative use of aprotinin have been found to be associated with VS.[5] Preoperative intravenous heparin, ACE inhibitors, and calcium channel blockers were found to be predictive in another study.[6] A meta-analysis investigating risk factors of VS post-cardiac surgery found that renal failure, previous cardiac surgery, pronged aortic cross-clamp and CPB time, combined surgery and increased red blood cell transfusion were associated with the risk of developing VS.[7]

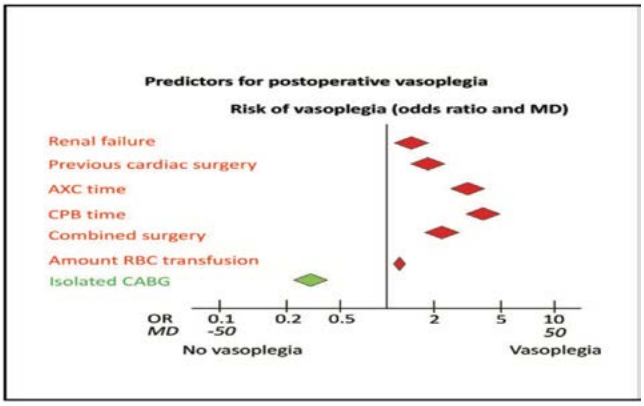

Figure 1: Risk factors of VS post cardiac surgery[7]
AXC – aortic cross-clamp, CPB – cardiopulmonary bypass time, RBC – red blood cell, CABG – coronary artery bypass graft

Management of vasoplegia

Recognition of at-risk patients forms the foundation of early management of VS. Early confirmation of symptoms of hypotension, low systemic vascular resistance (SVR), and normal/supranormal cardiac output are the basis of management. Mitigation for risk factors including early administration of antibiotics in sepsis-related VS is essential. Table I summarises pharmacological agents used in the management of VS. Management with a single agent often increases the risk of side effects; hence a combination of agents is sometimes used, particularly in intractable vasoplegia.[8]

Volume expansion and blood transfusion

Fluid resuscitation not exceeding 20–30 ml/kg coupled with blood product transfusion to correct anaemia is recommended. Excessive fluid resuscitation increases mortality.[4]

Catecholamine

Epinephrine, norepinephrine and dopamine have been used successfully in vasoplegic shock. Norepinephrine has shown a benefit in mortality and is recommended as a first-line agent, whilst dopamine is reported to have an increased risk of arrhythmias and mortality compared to others.[4,9] Norepinephrine is very potent in increasing mean arterial pressure (MAP) without increasing heart rate. It increases cardiac index through an increase in end-diastolic stroke volume achieved by mobilisation of splanchnic unstressed volume. Due to its lack of β2 adrenergic receptors, it does not increase lactate levels and can be used to guide resuscitation reliably. It preserves ventricular–arterial coupling through its action on cardiac β1 adrenergic receptors.[8]

Vasopressin

The benefits of vasopressin are particularly evident in catecholamine-resistant vasoplegia. It leads to membrane hyperpolarisation and can have a synergistic effect with catecholamines, leading to reduced rates and dosages. In the Vasopressin versus Norepinephrine in Patients with Vasoplegic Shock after Cardiac Surgery (VANCS) study comparing outcomes between vasopressin and norepinephrine, there was a significant

Table I: Vasoactive drugs for the management of vasoplegia[2]

Agent	Suggested dose	Advantages	Disadvantages	Evidence
Catecholamines norepinephrine	0.01–0.1 µg/kg/min continuous infusion	Increases MAP predominantly via increased SVR but may also provide inotropic support	High doses may be required to achieve haemodynamic goals in severe vasoplegia	Recommended first-line agent based on RCTs of septic shock May have mortality benefit over other catecholamines used in isolation
Phenylephrine	05–5 µg/kg/min continuous infusion	Increases MAP by increasing SVR	Few studies support its use as a single agent	Retrospectively associated with decreased survival compared with norepinephrine
Epinephrine	0.01–0.5 µ/kg/min continuous infusion	Increases MAP and provides inotropic support	Few studies focus on its use as a first-line agent for vasodilatory shock	Comparable in efficacy to combination of norepinephrine and dobutamine when both vasopressor and inotropic support required
Dopamine	0–20 µg/kg/min continuous infusion	Dose-dependent increases in SVR and inotropy	Increased risk of arrhythmia compared with other catecholamines	Meta-analysis of RCTs suggests increased risk of mortality compared with norepinephrine
Noncatecholamines vasopressin	1.2–6.0 U/h continuous infusion	Reduces catecholamine dose required to achieve MAP goal May reduce severity of renal failure	As a first-line agent, no significant mortality benefit compared with norepinephrine	Use is supported by several RCTs and the observation of severe vasopressin deficiency post-CPB
Terlipressin	1.3 µg/kg/h continuous infusion	Comparable with vasopressin but has a longer half-life	More selective than vasopressin for AVPR1 receptors, theoretically causing profound SVR increase and decrease in CO	Small studies suggest it is equally as effective as norepinephrine for raising MAP
Methylene blue	1.5–2 mg/kg bolus	In single boluses, may rapidly improve MAP in severe vasoplegia	May precipitate serotonergic syndrome and haemolytic anaemia and interferes with pulse oximetry	No high-quality RCTs investigating its use Retrospectively associated with mortality benefit when given early in vasoplegic shock
Hydroxocobalamin	5 g infusion over 5 min	Raises MAP and avoids some risks associated with methylene blue	More expensive than methylene blue Not well-investigated	Only described in case reports
Angiotensin II	Continuous infusion starting at 20 ng/kg/min	May dramatically improve MAP and reduce catecholamine requirements	Limited data May interfere with endogenous vasopressin synthesis	One recent RCT suggested haemodynamic improvement compared with placebo
Corticosteroids	Varies by study and drug of choice Hydrocortisone 50 mg q 6 h is frequently chosen	Likely hasten the resolution of shock	Not associated with mortality benefit in either septic shock or in non-vasoplegic cardiac surgery populations	No studies have specifically investigated their use in post-CPB vasoplegia
Vitamin C	6 g intravenous bolus per day	May hasten the reversal of shock when combined with hydrocortisone and thiamine	Limited safety and efficacy data	One recent retrospective study suggested haemodynamic and mortality benefit in septic shock patients

CO – cardiac output, RCT – randomised controlled trial, SVR – systemic vascular resistance, MAP – mean arterial pressure, AVPR1 – arginine vasopressin receptor 1

reduction in the composite endpoint of 30-day mortality or postoperative complications in the vasopressin group. This was supported almost exclusively by decreasing the occurrence of acute renal failure.[10]

Methylene blue

Methylene blue is an old agent that is reinventing itself. Therapeutic boluses of 1–2 mg/kg are given for 10–20 minutes, or up to one hour, with a terminal half-life of 5–6 hours. A continuous infusion of 1 mg/kg/hour up to 48–72 hours can be used to decrease the production of NO through inhibition of nitric oxide synthase (NOS). In a study comparing methylene blue and a placebo, its effect on systemic vascular resistance and mean arterial pressure improved significantly (Figure 2). Serotonin syndrome, haemolytic anaemia, and hypoxia due to pulmonary vasoconstriction are known side effects. Methylene blue has been recommended for use in the treatment of VSw after cardiac surgery, drug poisoning, anaphylactic shock, and post-liver transplantation.[11,12]

Corticosteroids

The use of corticosteroids is aimed at supplementing a depleted adrenal axis. Corticosteroid administration restores vascular responsiveness to vasopressors. The effects are thought to be through a non-genomic inhibition of the arachidonic acid cascade and a genomic inhibition of the nuclear translocation of the NF-κB transcription factor. Data on their effect on mortality is controversial, with some studies showing benefits while others fail to show benefits. There is some evidence of mortality benefits in cardiac surgery with the use of prophylactic dexamethasone. Hyperglycaemia, delayed wound healing, and an increased risk of gastrointestinal bleeding are notable adverse events.[13]

Ascorbic acid

Vitamin C production has been found to be diminished in critical illness. It is an important cofactor in the production of endogenous catecholamines biosynthesis. It cannot be produced endogenously and must be taken as a food supplement to maintain adequate levels. CPB has been shown to dilute and eliminate vitamin C. It is hypothesised that it increases adrenal deposits, increases catecholamine production, and increases sensitivity to catecholamines.[8,13]

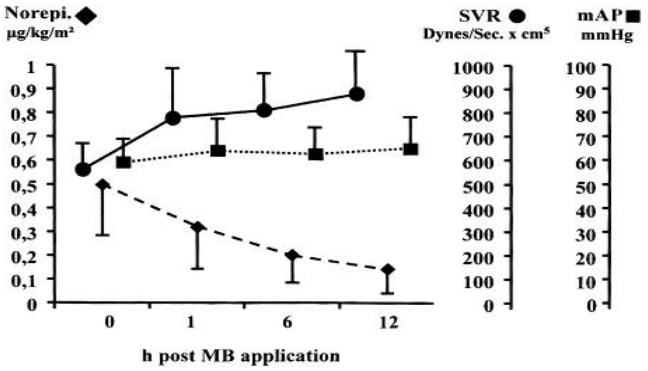

Figure 2: Haemodynamic response to methylene blue in VS[11]
MB – methylene blue, MAP – mean arterial pressure, SVR – systemic vascular resistance

Angiotensin II

Angiotensin II is produced through activation of the renin-angiotensin-aldosterone system. "Angiotensin II acts via many pathways, such as systemic and renal arteriolar vasoconstriction, increasing sympathetic activity, stimulating the release of endogenous vasopressin from the posterior pituitary gland, and the release of aldosterone from the adrenal gland. This stimulation produces direct arterial and venous vasoconstriction in the vascular smooth muscle, as well as an improvement in MAP regardless of adrenergic stimulation, in addition to improved vascular permeability."[4]

Hydroxocobalamin

Hydroxocobalamin is a precursor of vitamin B_{12}. It has become an emerging agent in the treatment of VS in an off-label capacity. B_{12} inhibits guanylate cyclase and is a scavenger for NO.[14] The optimal dose for use is unknown, with reports of bolus doses of 5 g for 10–15 minutes per day in case reports.

Selepressin

Although there was a lot of anticipation for the effects of selepressin in VS, results have been disappointing. Selepressin, an investigational selective vasopressin agonist, was tested in 828 patients with septic shock receiving moderate-dose norepinephrine. Patients were randomised to an additional selepressin or placebo treatment with no difference in outcomes between groups. There was a decrease in dosage of norepinephrine but no difference in mortality, ventilator-free days, vasopressor-free days, or ICU-free days.[15]

Potential new strategies

Vasopressor combinations

Individual vasopressors, at high doses, may lead to a risk of increased incidents of adverse events. Combinations of vasopressors, that work at different receptors, may alter the efficacy/risk ratio, and reduce doses of each and improve safety. Combination therapy leads to significantly less vasopressor use.[16]

Very high doses of norepinephrine

Although some literature may suggest a norepinephrine cut-off value ranging from 0.5–2 µg/kg/min, they have been associated with excess mortality. New evidence points to a cut-off value of 1 µg/kg/min. Higher doses were associated with a mortality of 86% in patients with a SOFA score > 10 and with a mortality of 58% in patients with a SOFA score < 10.[16]

Pharmacogenomics

Gene polymorphism, which in part informs pharmacogenomics, has shown altered responses to individuals with genomic

variants. This affects the efficacy and safety of drugs used including norepinephrine, epinephrine, vasopressin, and corticosteroids.[17]

Modulation of the sympathetic system

α2 agonists

Administration of α2 agonists, in animal studies, was used to reduce the central sympathetic activity, and restore the response to vasoconstrictors such as α1 agonists or angiotensin II. This attempt was at reducing the inappropriate sympathetic response and thereby avoiding the associated receptor desensitisation. Alpha-2 agonists also have a direct vasoconstrictor effect. Dexmedetomidine is one such drug agent.[18]

Selective β1 blockade

Selective β1 blockers such as esmolol are postulated to restore vascular responsiveness to vasopressors, reducing heart rate and the dose of norepinephrine. The decrease in heart rate was associated with improved arterial elastance, and an improved ventricular–arterial coupling.[19]

Adrenomedullin blocking

Adrenomedullin supplementation has been shown to improve endothelial barrier function, attenuate systemic inflammation, and reverse hypodynamic circulation and pulmonary hypertension in subclinical endotoxaemia. Controversially, it has also been associated with mortality in septic patients.[20]

Conclusion

At a rate of up to 35%, VS is common. It may present with differing levels of hypotension ranging from a drop of > 20% of baseline to refractory hypotension. Therapies range from single, standard therapies to multimodal therapies. Some therapies that are traditionally used as intravenous agents have been used off-label as inhaled agents.

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