REVIEW ARTICLE

Kounis syndrome: a narrative review

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Inflammatory mediators released from activated mast cells and basophils during hypersensitivity reactions have direct pathological effects on the myocardium and coronary vasculature. It was traditionally thought that cardiovascular signs and symptoms in anaphylaxis are largely due to peripheral vasodilation and increased vascular permeability. However, there is extensive evidence of primary cardiac involvement during hypersensitivity reactions, most notably coronary vasoconstriction as well as atherosclerotic plaque erosion and rupture, leading to angina pectoris and acute coronary syndromes. Furthermore, mast cells are well established as effector cells in atherosclerosis, through their effects on atherosclerotic plaque progression and destabilisation. It was noted over 30 years ago that cardiac patients have a markedly higher concentration of biologic amines (especially histamine) in their coronary vasculature, and, additionally, are hyper-reactive to the effects thereof. This is borne out by the disproportionate mortality rate of those with cardiac disease that suffer a hypersensitivity reaction. Kounis syndrome refers to angina pectoris or an acute coronary syndrome secondary to a hypersensitivity reaction, with the subtypes dependent on the underlying state of the coronaries and presence of a drug-eluting stent or not. This review will focus mainly on the aetiology, pathophysiology, diagnoses and treatment of this important syndrome.

Keywords: acute coronary syndromes, allergic angina, allergic myocardial infarction, anaphylaxis, Kounis syndrome

Introduction

There is extensive evidence of cardiac involvement in animal (*in vivo* and *in vitro*) anaphylaxis[1–3] as well as human anaphylaxis.[4–7] During anaphylaxis, the heart is both a source and a target of released chemical mediators, which have direct effects on the coronary vasculature and myocardium.

Kounis syndrome is the concurrent occurrence of acute coronary syndromes with hypersensitivity reactions (including anaphylaxis).[8] Two principal variants of the syndrome are described: type 1 is allergy-related angina due to coronary spasm with type II being allergy-related myocardial infarction due to plaque rupture and thrombus formation. Drug-eluting stent thrombosis (late stent thrombosis) secondary to hypersensitivity reactions has recently been proposed as a third type.[9]

Historical background (see Figure 1)

Paul Ehrlich published his seminal description of mast cells in 1878.[10] Anaphylaxis was characterised by Richet and Portier in 1901, which won Richet the Nobel Prize in 1913.[11] In 1913 Auer reported ECG changes during animal anaphylaxis.[12]

The first case of myocardial infarction during an allergic reaction in humans was reported in 1950.[13] In 1991, Kounis and Zavras described a 'syndrome of allergic angina' as the simultaneous occurrence of chest pain and allergic reactions, accompanied by clinical and laboratory findings of angina pectoris, caused by inflammatory mediators released during the allergic process.[8] Kovanen in 1995 found much greater coronary mast cell degranulation at the sites of erosion or plaque rupture than in adjacent areas;[14] later Braunwald noted that mediators such as histamine or leukotrienes released during allergic reactions could induce vasospastic angina by acting on coronary smooth muscle.[15]

In 2002, two variants of the original 'allergic angina syndrome' were described,[16] with drug-eluting stent (DES) thrombosis later proposed as a third type.[9,17] It was first reported in children in 2009, including in a two-year-old.[18–20]

Epidemiology

The lifetime prevalence of anaphylaxis is at least 1.6%, probably higher.[22] It is increasing in developing countries,[23–25] and leading to an increased number of UK critical care admissions.[26]

Perioperative anaphylaxis occurs in 1:3 500–1:20 000 cases, with a mortality of 9%.[27] It accounts for 9–19% of anaesthetic-associated complications and 5–7% of deaths during anaesthesia.[27,28] The most common agents implicated in perioperative anaphylaxis are neuromuscular blocking agents (58%), latex (19.6%) and antibiotics (12.8%).[29]

It is difficult to estimate the incidence of Kounis syndrome. It is probably under-reported, with anaesthesiologists and intensivists generally unaware of the condition. It is not unlikely to occur though. Two out of 21 healthy adults developed symptoms and ECG changes suggestive of myocardial ischaemia during a diagnostic sting challenge.[30] In a French survey of anaphylaxis under anaesthesia, 73.6% of cases had cardiovascular involvement.[31] A Swiss study showed an incidence of severe life-threatening anaphylaxis with circulatory signs of 7.9–9.6 per 100 000 people per year.[6] Many cases go unreported, although awareness and reporting is increasing.

Aetiology

Sixty years ago, Pfister reported a case of antero-septal myocardial infarction and urticaria four days after treatment with penicillin.[13] Hundreds of cases of Kounis syndrome have been described since, including several case series.[32–35]
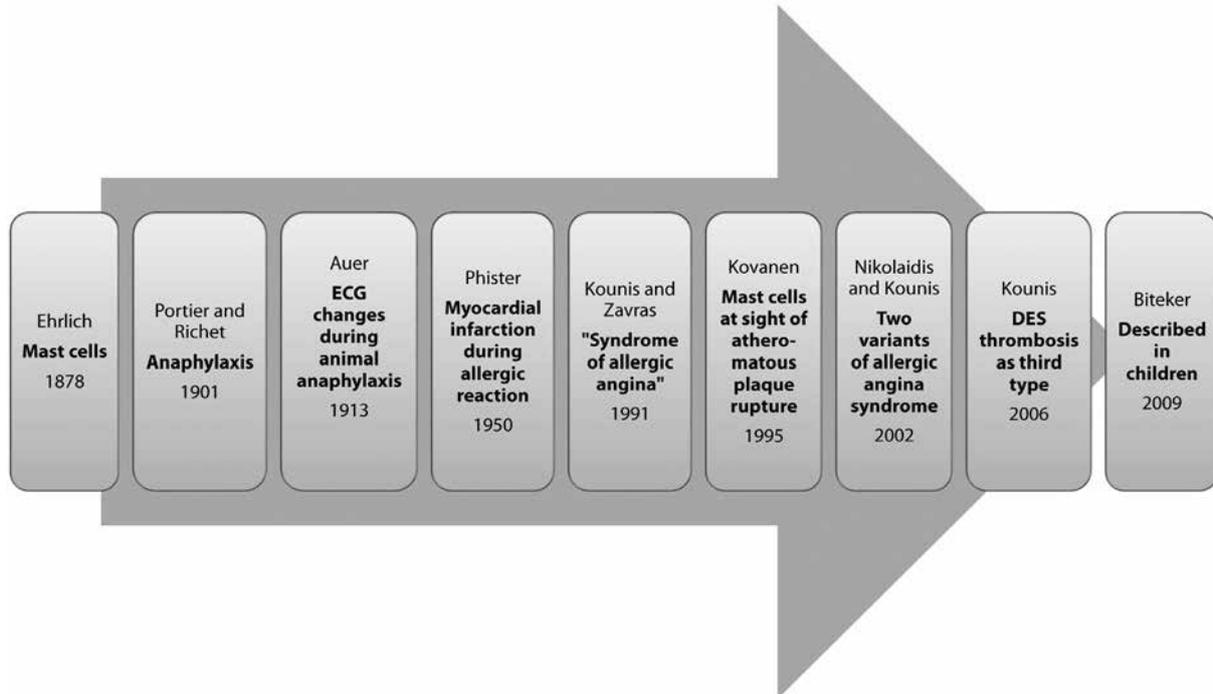
Figure 1: Timeline of Kounis syndrome.[21]

Kounis syndrome has been described secondary to a large number of drugs, of various classes (e.g. antibiotics, muscle relaxants, anti-neoplastics, contrast media, NSAIDS, thrombolytics etc.).[21,36,37]

Several environmental exposures are linked to the syndrome (with Hymenoptera stings accounting for the majority of serious reactions); in addition, there are a number of diseases and conditions related to Kounis syndrome (e.g. mastocytosis, bronchial asthma etc.).[36]

One can argue that any drug or condition able to provoke an allergic reaction can lead to Kounis syndrome. It is well known that atopic individuals are at higher risk of acute coronary syndromes.[38–40]

Pathophysiology
Anaphylaxis is a serious, potentially fatal, multi-organ syndrome caused by a triggered release of mast cell derived mediators into the systemic circulation.[41,42] The trigger is either (1) immunologic (IgE or IgG dependent) or (2) non-immunologic (direct stimulation of mast cells by certain drugs, cold air, exercise, etc.).[43–46]

The immunologic pathway involves an allergen-induced crosslinking of IgE antibodies (formed during a clinically silent initial exposure) coupled to mast cells and basophils, which induces a transduction cascade activating mast cells. Note that a very small amount of allergen is needed to trigger the cascade.[47]

Activated mast cells degranulate and release an array of vasoactive and pro-inflammatory mediators, namely (1) preformed granule associated mediators, (2) newly generated lipid-derived mediators plus (3) cytokines and chemokines (Table 1).[48–51]

Mast cells are widely distributed in tissues, particularly those with external environment contact (i.e. skin, gastrointestinal system, lung) but also in other organs such as the heart.[49] In the heart they are located mainly between myocardial fibres (in close proximity to myocytes), around both large coronary vessels and small intramural coronary arteries, and in the arterial intima and adventitia.[49,51,52]

Uniquely, heart mast cells can be directly activated by non-allergenic stimuli (e.g. anaphylatoxins C3a and C5a and substance P),[49,53] as well as by drugs such as muscle relaxants, protamine and radio-contrast media.[54] Cardiac mast cells are some of the most important effector cells of anaphylaxis.[50,55]

Effects of mast cell mediators on coronary circulation:
Histamine has important context-specific effects on cardiac tissues. It dilates coronary arteries (via H_1-receptors on vascular smooth muscle cells) and causes arrhythmias and atrio-ventricular conduction blocks in healthy volunteers.[56] It further leads to a baroreceptor-mediated tachycardia by decreasing mean aortic pressure.[57]

However, in patients with coronary artery disease and vasospastic angina, intravenous histamine causes a decrease in coronary blood flow, and in some cases severe coronary spasm.[56,58]

Histamine also induces tissue factor expression in endothelial cells and vascular smooth muscle cells, thus mediating thrombus formation in acute coronary syndromes.[59]

Heart mast cells release large quantities of *chymase* (compared with lung and skin), as well as significant quantities of *renin*,[2,60] activating the cardiac renin-angiotensin-aldosterone system.

Table 1: Mediators released by activated human mast cells (clinically important ones italicised)

Preformed mediators
• *Histamine* • *Tryptase* • *Chymase* • *Renin* • *Endothelin* • Carboxipeptidase • Heparin proteoglycan • Chondroitin sulfate proteoglycan • Cathepsin G
Newly generated lipid-derived mediators
• *Platelet activating factor* • *Leucotriene (LT) B4, LTC4, LTD4, LTE4* • *Prostaglandin (PG) D2, PGE2* • *Thromboxane*s
Cytokines and chemokines
• Inflammatory cytokines (interleukin (IL)-4, IL-5, IL-6, IL-13, tumour necrosis factor-α) • Chemokines (monocyte chemotactic protein-1, IL-8, RANTES*) • Hematopoietic factors (IL-3, granulocyte-macrophage colony-stimulating factor) • Growth factors (vascular endothelial growth factor, platelet derived growth factor etc.)

*Regulated on activation, normal T cell expressed and secreted.

Chymase has potent angiotensin-converting enzyme (ACE) activity, even in the presence of ACE inhibitors.[60] Angiotensin is a coronary vasoconstrictor, causes arrhythmias and leads to fibrosis and apoptosis.

Platelet activating factor (PAF) causes a significant decrease in coronary blood flow and marked negative inotropy; it also has a direct arrhythmogenic effect.[61] It may also contribute to atherosclerotic plaque instability and rupture by inducing local platelet aggregation and the release of lytic enzymes by macrophages.[14] Systemic PAF causes peripheral vasodilatation.[62] One of the major causes of disseminated intravascular coagulation in fatal anaphylaxis is PAF-induced platelet activation.[63] Of note, PAF has shown significant correlation with the severity of anaphylaxis, better than either histamine or tryptase.[64,65]

Intravenous or intra-coronary infusion of *cysteinyl leukotrienes*, such as leukotriene D4, leads to a rapid and sustained rise in coronary vascular resistance and subsequent decrease in coronary blood flow.[66,67]

Thromboxane causes vasoconstriction and is an important mediator of platelet aggregation.[68] In experimental animal studies, *prostaglandin D2* causes coronary vasoconstriction and arrhythmias.[69]

Mast cells in cardiovascular disease

There is increasing evidence of the central role of mast cells and their mediators in cardiovascular disease, through their effects on atherosclerotic plaque progression and destabilisation.[52,70,71]

Histamine and tryptase may contribute to fatty streak formation and the generation of unstable plaques susceptible to rupture.[52] Activation of matrix metalloproteinases by mast cell derived proteases is an important mechanism in atherosclerotic plaque destabilisation.[72]

Higher levels of histamine are found in coronary arteries of patients who died from ischaemic heart disease.[73] They also have more degranulated mast cells at the site of atheromatous rupture, compared with adjacent normal intima.[14,52] Patients with peripheral vascular disease were found to have higher plasma levels of histamine compared with controls.[74] Mast cell derived mediators like histamine, serotonin, leukotrienes and prostaglandin D2 contribute to vascular responsiveness; increased numbers of mast cells are associated with coronary vasospasm.[75]

Some authors have suggested using tryptase as a biomarker for atherosclerosis[76] and acute coronary syndromes.[77–79] Pre-existing cardiovascular disease, mastocytosis and elevated baseline serum tryptase are all risk factors for fatal anaphylactic reactions.[80,81]

Hypersensitivity-induced coronary stent thrombosis (Kounis type III)

All the components of drug-eluting stents, namely (1) the metal strut (composed of nickel, molybdenum and chromium),[82] (2) the polymer[83] and (3) the impregnated paclitaxel/sirolimus,[84] can elicit hypersensitivity reactions with a release of pro-thrombotic mediators like PAF, cytokines and chemokines. Several hundred cases of hypersensitivity reactions related to drug-eluting stents (DES) have been reported, some of which were fatal.[85]

Based on human autopsy series, DES late/very late stent thrombosis is caused by impaired arterial healing (with characteristic incomplete re-endothelialisation, persistent fibrin deposition and macrophage infiltration) when compared with bare metal stents.[86] Autopsies confirmed inflammatory cell infiltrates (plasma cells, macrophages, eosinophils and lymphocytes) that permeate all three vascular wall layers, a histopathological picture very similar to Kounis type I and type II.[86]

Clinical variants

Systemic allergic signs and/or symptoms accompanied by clinical, electrocardiographic or laboratory findings of myocardial ischaemia constitutes Kounis syndrome.[8] Three variants have been described (Table 2).[9,16,85]

Table 2: Clinical variants of Kounis syndrome

Clinical variant	Pathogenesis
Type I: vasospastic allergic angina	Patients with *normal or nearly normal coronary arteries* without risk factors for coronary atherosclerosis in which acute release of inflammatory mediators causes *coronary spasm*; (1) either without a rise in cardiac enzymes or (2) coronary spasm leading to an acute myocardial infarction (raise in cardiac enzymes). This may be due to endothelial dysfunction or micro-vascular angina
Type II: coronary thrombosis leading to allergic myocardial infarction	Patients with *underlying coronary atherosclerosis* in which inflammatory mediators causes either coronary spasm (with normal cardiac enzymes) or coronary spasm and plaque erosion or rupture leading to an acute myocardial infarction
Type III: coronary artery drug-eluting stent thrombosis	Hypersensitivity reaction to one of the components of the stent causing thrombosis. Giemsa and haemotoxalin-eosin staining shows *mast cells and eosinophils* respectively in the aspirated stent thrombus

Table 3: Clinical severity scale of immediate hypersensitivity reactions[47]

Grade	Clinical signs
I	*Muco-cutaneous signs*: erythema, urticaria ± angioedema
II	*Moderate multi-visceral signs*: muco-cutaneous signs ± hypotension ± tachycardia ± dyspnoea ± gastrointestinal disturbances
III	*Life-threatening mono- or multi-visceral signs*: cardiovascular collapse, tachycardia/bradycardia ± arrhythmias ± bronchospasm ± muco-cutaneous signs ± gastrointestinal disturbance
IV	*Cardiac arrest*

Diagnosis

There are two aspects to the diagnosis: the hypersensitivity reaction plus the myocardial ischaemia. Dewachter suggested a triad of evidence to diagnose perioperative anaphylaxis (clinical, biologic and allergologic evidence).[47] It is important to actively look for and anticipate cardiac involvement if anaphylaxis is suspected or diagnosed.

Clinical/ECG features

The modified Ring and Messmer clinical severity scale should be used to classify signs and symptoms of immediate hypersensitivity reactions (Table 3).[11,47,87]

The diagnosis of anaphylaxis during anaesthesia can be challenging, because important features like hypotension or bronchospasm have many other, more common causes.[88] Note that cutaneous signs can be absent in rapidly progressing anaphylaxis, further clouding the diagnosis.

ECG changes are integral to the diagnosis of Kounis syndrome, in combination with the clinical picture and biochemical markers. The syndrome usually presents with changes in the anterior or inferior leads, the right coronary artery being commonly involved.[21]

It may also show non-specific ST-segment/T-wave abnormalities, atrial fibrillation, nodal rhythms, ventricular ectopics, bigeminy, QRS-complex broadening and QT-segment prolongation; rarely do patients have a normal ECG.

Special investigations

- *Cardiac*: Cardiac enzymes (troponins) should be sent as soon as cardiac involvement is suspected. Other blood tests such as d-dimer, full blood count, brain natriuretic peptide and serum cholesterol levels can be sent after the acute event.

Transthoracic or trans-oesophageal echocardiography can reveal regional wall motion abnormalities suggestive of acute coronary syndromes, and can help distinguish between other causes of chest pain and/or hypotension (such as aortic dissection, pericarditis, pericardial effusion and pulmonary embolism).

Coronary angiography will distinguish between types I and II Kounis syndrome, as well as being useful to guide therapy (e.g. intracoronary calcium channel blockers for vasospasm).

- *Hypersensitivity reaction*: Tryptase, histamine levels, specific IgE antibody and eosinophil levels will help to identify an allergic reaction.

Mast cell tryptase is elevated in most patients with systemic anaphylaxis (though not all). Tryptase peaks at 1–1.5 hours after anaphylaxis onset and remains elevated for over 5 hours. The best time to measure is from 1–2 hours, but no longer than 6 hours after onset. Histamine has a half-life of less than 30 minutes[89] and is thus not commonly measured.

Although PAF correlates better with the severity of anaphylaxis than histamine or tryptase,[64,65] the extremely short half-life precludes its clinical use.[48]

Anaphylatoxins like C5a can cause mast cell degranulation,[90] thus complement levels may be useful.

Allergologic testing

Allergy testing, such as patch testing, skin prick, intradermal testing and serum-specific IgE testing for IgE antibodies should be done 4–6 weeks after the reaction (to avoid false negative test results because of mast cell depletion). However, mast cells can degranulate from direct stimulation (e.g. morphine, codeine), leading to the absence of IgE antibodies.[91]

It should be performed based on clinical history, with the aim to prove the pathophysiological mechanism and identify a culprit to avoid next time.

Treatment

At present there are no clear treatment guidelines for Kounis syndrome; most of the data are derived from case reports. Two aspects need treatment, (1) the allergic reaction and (2) the acute coronary syndrome (ACS). Treating the hypersensitivity reaction may abolish the type I variant, but the type II variant often needs ACS treatment in addition.

Allergic reaction/anaphylaxis

The World Allergy Organization recently published a consensus document summarising the evidence-based anaphylaxis guidelines developed and published independently from 2010 to 2014 by four allergy/immunology organisations.[92] More specifically, there are numerous protocols for perioperative anaphylaxis.[93,94] It is recommended to follow one of these.

The first-line pharmacologic treatment is prompt injection of adrenaline,[92,95] although this is not supported by any randomised controlled trial.[95,96] In addition to the cardiovascular and respiratory beneficial effects, it suppresses further mediator release from mast cells and basophils during anaphylaxis (via β_2-adrenergic receptors).[97] The therapeutic plasma concentration of adrenaline for successful treatment of anaphylaxis is unknown. However, one should titrate small intravenous boluses to clinical effect, the dose depending on clinical presentation (using the Ring and Messmer grading scale).[88,98,99] Some authors suggest never using adrenaline in grade I reactions.[47]

IV fluids (crystalloids) should be given to compensate for the intravascular loss, as up to 35% of the intravascular volume can leak into the extravascular space within 10 minutes.[100]

Although most guidelines advocate the use of anti-histamines and glucocorticoids, no robust studies confirming the effectiveness of these treatments exist.[95,101] However, in those with type I variant and milder grades of anaphylaxis, hydrocortisone (1–2 mg/kg/day) and H_1 plus H_2-antihistamines (diphenhydramine 1–2 mg/kg and ranitidine 1 mg/kg) may be adequate treatment.[102]

Refractory anaphylaxis should be managed with a continuous infusion of vasopressors rather than IV boluses, but only by those experienced with their use.[103] In addition, vasopressin,[104–106] glucagon,[107,108] anti-cholinergic drugs (atropine), methylene blue,[109] and α_1-agonists[110–112] are all proposed treatments for refractory cases.

Acute coronary syndromes

The treatment of acute coronary syndromes is based on the latest ACC/AHA guidelines, and will depend on the presentation.[113,114] In those with an ST-elevation myocardial infarction (STEMI) the focus is on obtaining an urgent angiogram, with subsequent management dependent on findings (medical therapy, percutaneous coronary intervention or coronary artery bypass grafting). Note that fibrinolytics like streptokinase carry a high risk of anaphylaxis.[115]

Anaphylaxis guidelines suggest using 100% O_2, but routine oxygen administration in myocardial infarction may be associated with increased mortality.[116] Oxygen should thus be titrated to normoxia.

Though nitroglycerin may be used for ischaemic pain, it can worsen the hypotension of anaphylaxis and should be used cautiously.

Opioids such as morphine, codeine and pethidine can induce mast cell degranulation and aggravate allergic reactions. Fentanyl and its derivatives (with minimal mast cell activation) may be better-suited narcotic analgesics.

β blockers offset the beneficial effects of adrenaline in anaphylaxis and should be used with extreme caution, if at all. Glucagon can be used for patients with anaphylaxis and hypotension who are on β blockers.[107]

Long-acting calcium channel blockers (CCB) and nitrates are generally recommended for patients with hypersensitivity-induced coronary vasospasm.[102] Based on the pathophysiology of Kounis syndrome, CCB may be considered as the initial anti-ischaemic drugs of choice.

Uncoated aspirin should be given to all patients promptly after presentation. However, aspirin and NSAIDS are two of the most common causes of drug-induced anaphylaxis. Aspirin influences the pathogenesis of anaphylaxis through cyclooxygenase inhibition, by shunting arachidonic acid into the leukotriene pathway, producing more anaphylaxis mediators.[117]

In the type III variant, in addition to ACS treatment, aspiration of the intra-stent thrombus should be considered, followed by histological examination of the clot (staining for mast cells and eosinophils).[102]

Based on pathophysiological findings, mast cell blockers have been proposed as potential therapeutic agents.[70,71] Disodium cromoglycate seems ineffective; however, the flavonoid quercetin showed some promise.[118] Mast cell stabilisation may be an important future therapeutic option for Kounis syndrome.

Controversies regarding adrenaline

The use of adrenaline in anaphylaxis is based on a century of clinical experience, epidemiological studies,[119] fatality studies[81,120,121] and prospective studies,[4,30,122] as well as in-vitro[123] and animal studies.[103,104,124]

Delayed administration of adrenaline in anaphylaxis is associated with increased mortality.[81,120,121,124] Furthermore, animal models suggest that giving adrenaline in *established* anaphylactic shock does not hasten recovery, and may cause LV impairment.[124,125] In practice it is a difficult balance between timeous administration to those needing it and avoiding it for low-grade anaphylactic reactions.

Apical ballooning syndrome (ABS), or Tako-Tsubo cardiomyopathy (a reversible left ventricular dysfunction) is thought to be a result of excess catecholamine stimulation of the heart, with several pathophysiological postulates (epicardial coronary artery spasm,

microvascular spasm, or direct myocyte injury).[126] There are several reports in the literature of ABS following adrenaline therapy during anaphylaxis.[127–134]

While it is the first-line therapy in anaphylaxis, its use in acute coronary syndromes is a slightly more challenging decision. It can cause serious side effects like arrhythmias (e.g. tachycardia leading to aggravated myocardial ischaemia), hypertension (causing intra-cerebral bleeds, pulmonary oedema etc.) and coronary vasospasm. Elderly patients and those with a history of hypertension, peripheral vascular disease, ischaemic heart disease and untreated hyperthyroidism are especially prone to these side effects.[135] A study looking at fatal anaphylaxis attributed 3 out of 20 (15%) deaths directly to adrenaline overdose.[120]

Adrenaline is not an innocuous drug in anaphylaxis. It has a narrow therapeutic index[97], and should be carefully titrated to effect.

Prognosis

This will depend on the magnitude of the initial reaction, which in turn depends on the patient's sensitivity (i.e. previous exposure), other comorbidities (e.g. pre-existing coronary atherosclerosis[80,81,136] and mastocytosis[39,137,138]), the site of antigen–antibody reaction, the allergen concentration and the route of allergen entrance (e.g. intravenous versus topical).

The prognosis is generally good beyond the acute phase, with left ventricular function recovering over three days to several weeks. In the acute phase patients may develop life-threatening arrhythmias, pulmonary oedema and plaque rupture leading to a coronary thrombus, but fortunately death is rare.[139]

There are some reports that the type I variant of Kounis has a better prognosis than type II.[33]

Conclusions

Mediators released from cardiac mast cells during a hypersensitivity reaction are key to the subsequent adverse CVS effects. It would be prudent to actively look for cardiac involvement whenever hypersensitivity is suspected, keeping in mind that patients with cardiovascular disease have a significantly higher risk of developing severe or fatal anaphylaxis.[80,81] Additionally, commonly used CVD drugs such as β blockers and ACE inhibitors could exacerbate anaphylaxis and make it resistant to treatment.[140]

Adrenaline remains the first-line treatment for higher-grade anaphylaxis. However, in those with CVD (and specifically ACS) it needs to be carefully considered, weighing the side effects of adrenaline against the risks of untreated anaphylaxis. There is scope to develop multispecialty guidelines to manage this complex condition.

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