



Anaphylaxis and cardiovascular diseases: a dangerous liaison

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Purpose of review

Anaphylaxis is a life-threatening event in which the cardiovascular system is responsible for the majority of clinical symptoms and for potentially fatal outcome. This review summarizes the most recent clinical and experimental data on cardiovascular involvement during anaphylaxis.

Recent findings

Great efforts have been made in the last few years to understand the pathophysiology of anaphylactic reaction and to provide better identification of risk factors for the development of this reaction. Coronary blood flow can be impaired during anaphylaxis, which may significantly contribute to an unfavourable outcome. Also, preexisting coronary artery disease is a negative prognostic factor for anaphylaxis. In addition, acute ischemic events, including angina and myocardial infarction, are currently considered as part of the clinical picture of anaphylaxis. Moreover, cardiac emergency can be the presenting clinical picture of mast cell-related disorders.

Summary

Both cardiovascular and allergic diseases are frequent among populations. A better understanding of the mechanisms leading to cardiac mast cell activation and the effects of mast cell mediators on cardiovascular system can help improve the prevention and treatment of anaphylaxis.

Keywords

anaphylaxis, heart, mast cell, mediators

INTRODUCTION

Allergic diseases are a major health problem worldwide, and their prevalence is expected to increase in the next few years [1]. Anaphylaxis is the most severe clinical presentation of allergy and is frequently a medical emergency in both pediatric and adult patients [2]. Systemic anaphylaxis is a relatively rare condition with a lifetime prevalence estimated to be 0.05–2% [3] and a mortality rate ranging from 2 to 20% [4]. Data from epidemiological studies in the United Kingdom clearly demonstrate that the rate of anaphylaxis in the general population has almost doubled in the last 5 years [5].

Anaphylactic shock is a classical example of cardiovascular involvement in allergic patients. Central (cardiac) and peripheral vascular symptoms dominate the clinical picture and are often the leading cause of death [6]. Although the skin (urticaria and angioedema), the lung (laryngeal edema and bronchospasm) and the gastrointestinal system (abdominal pain, nausea, vomiting and diarrhea) are mainly involved in the early stages of

anaphylaxis, dysfunction of the cardiovascular system is usually responsible for the fatal outcome of anaphylactic events [7]. Cardiovascular manifestations of anaphylaxis include hypotension and shock, cardiac arrhythmias, ventricular dysfunction and cardiac arrest [8]. Major advances have been made in the last few years to understand the pathophysiology of anaphylactic reaction and to provide better identification of risk factors for the development of fatal anaphylaxis. Recent observations indicate that coronary blood flow can be impaired during anaphylaxis, which may significantly

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KEY POINTS

- Involvement of the cardiovascular system and preexisting cardiovascular disorders are strongly associated with fatal or near-fatal anaphylaxis.
- Mast cell-derived mediators, such as histamine, prostanoids and platelet activating factor (PAF), can reduce coronary blood flow, depress myocardial contractility and induce arrhythmias and cardiac arrest, all major features of fatal anaphylaxis.
- Severe allergic reactions are a cause of acute coronary syndromes, including angina and myocardial infarction (Kounis syndrome).
- A cardiac emergency, including cardiac arrest, may be the presenting symptom of a mast cell-related disorder even in the absence of other signs of the disease.

contribute to an unfavourable outcome [9,10]. In addition, acute ischemic events, including angina and myocardial infarction, are currently considered as part of the clinical picture of anaphylaxis [11]. A preexisting coronary artery disease is a negative prognostic factor for anaphylaxis [12]. This is a very important issue to keep in mind because procedures for myocardial revascularization, requiring administration of radiocontrast media, are expected to increase steadily over the next few years. In addition, new agents (antihypertensive and anticoagulants) and devices (drug-eluting stents), potentially capable of inducing a type I adverse reaction, are being introduced in the cardiology practice. Thus, the chance that anaphylaxis may occur in patients with ischemic heart disease is expected to increase in the near future.

HEART AS A SOURCE AND TARGET OF INFLAMMATORY MEDIATORS

Anaphylactic reactions are frequently associated with cardiovascular alterations that are often transient, but in some cases, they may result in extensive and life-threatening myocardial damage. The human heart, under normal conditions, contains a large number of mast cells predominantly located within adventitia of large coronary vessels and around small intramural coronary arteries [13]. The number of mast cells is dramatically increased in the heart of patients with ischemic heart disease and dilated cardiomyopathies. In-vivo studies on biopsies and autopsies from patients with ischemic heart disease confirmed that mast cells are particularly enriched within atherosclerotic plaques [14]. Thus, cardiac mast cells activated during anaphylaxis release mediators at sites that are crucial for

causing alterations in coronary blood flow. Histamine, which is released in large quantities during anaphylaxis, induces a rapid decrease in the mean aortic pressure and an increase in coronary blood flow [15]. However, in patients with coronary artery disease, intravenous injection of histamine caused a response completely different from that elicited in noncoronary patients and rather induced a decrease in coronary blood flow associated sometimes with large coronary artery spasm [16]. Histamine has also been shown to induce tissue factor expression in endothelial cells and vascular smooth muscle cells [17], leading, in turn, to thrombin formation and activation of the coagulation cascade. Thus, histamine not only is responsible for peripheral vascular changes of anaphylactic shock but may be involved in coronary alterations and local thrombotic changes that are frequently observed in fatal anaphylaxis.

Cysteinyl leukotrienes LTC₄, LTD₄ and LTE₄ exert profound myocardial and coronary effects. Intravenous or intracoronary infusion of LTD₄ in humans causes a rapid and sustained increase in coronary vascular resistance with reduction of coronary blood flow [18,19]. Coronary smooth muscle cells express both the CysLT₁ and the CysLT₂ receptors, and it is currently not known whether coronary constriction is mediated by one or both the receptors. In addition, both CysLT receptors are expressed on specialized cells of the cardiac conduction system, primarily on Purkinje cells. Blockade of cysteinyl leukotriene biosynthesis in patients undergoing coronary catheterization and angioplasty prevents the development of myocardial depression and repolarization changes induced by the procedure [20]. These observations confirm the potentially deleterious role of leukotrienes on myocardial function and cardiac rhythm. The cardiovascular effects of PGD₂ in humans are not known; however, studies in experimental animals indicate that this eicosanoid induces coronary constriction and arrhythmias in isolated perfused hearts [21]. This negative effect may contribute to myocardial depression and impaired ventricular function, which are main hemodynamic events of the anaphylactic shock.

PAF was initially identified as a lipid mediator inducing platelet aggregation and degranulation [22,23]. PAF in the heart can be released not only by mast cells but also by basophils, neutrophils, eosinophils and tissue macrophages [23,24]. PAF causes a severe reduction of coronary blood flow and a significant depression of myocardial contractility. This mediator has a direct arrhythmogenic effect because of its capacity to interact with ionic channels on myocytes [25]. In addition to

these hemodynamic effects, PAF promotes the recruitment and activation of neutrophils and eosinophils within the cardiac tissue [26]. More importantly, PAF, generated by mast cells infiltrating the atherosclerotic plaque, may contribute to its instability and rupture by inducing local platelet aggregation and release of lytic enzymes by macrophages [27]. PAF released within systemic circulation induces peripheral vasodilation with relative hypovolemia and severe hypotension [26]. In addition, PAF-induced platelet activation is a major cause of disseminated intravascular coagulation (DIC), frequently associated with fatal anaphylaxis [28]. Together these observations suggest that PAF is a mediator capable of reproducing most, if not all, hemodynamic dysfunctions of severe anaphylaxis. Interestingly, patients with systemic anaphylaxis have elevated plasma levels of PAF that significantly correlate with the severity of anaphylaxis. Moreover, patients with food-induced fatal anaphylaxis have reduced plasma levels of acetylhydrolase, the enzyme responsible for PAF degradation, as compared with those with nonfatal anaphylaxis or normal individuals [29]. These observations strongly support a primary role of PAF in the cardiovascular manifestations of anaphylaxis and suggest that a deficiency in the enzymatic system involved in PAF degradation may be a risk factor for severe anaphylaxis.

Chymase, a neutral peptidase stored within mast cell granules, has angiotensin-converting enzyme (ACE) activity and is able to convert angiotensin I into angiotensin II. The release of this enzyme from cardiac mast cells is crucial for activation of the cardiac renin-angiotensin system (RAS) and may further contribute to myocardial dysfunction during anaphylaxis.

Thus, from the studies mentioned above, there is clear evidence that mediators secreted from cardiac mast cells exert multiple and often redundant effects on myocardial function, electrical activity and coronary blood flow (Fig. 1). These effects profoundly influence cardiac and peripheral vascular responses and lead to the major clinical features of anaphylaxis, such as shock, myocardial ischemia, arrhythmias and sudden cardiac death.

CARDIOVASCULAR SYMPTOMS DURING ANAPHYLAXIS

Cardiovascular symptoms in typical anaphylaxis are less frequent than cutaneous or respiratory manifestations, but they greatly influence the severity of the reaction. Chest pain, hypotension, collapse, shock, loss of consciousness, tachycardia or arrhythmias are typical features of cardiac anaphylaxis. Coronary

arteries can be involved and a reduced coronary flow may contribute to the onset of symptoms and to a poor outcome. Cardiac arrest is rare, but it is a leading cause of death in fatal anaphylaxis. Skin involvement is the most common clinical finding of anaphylaxis, and urticaria or angioedema, pruritus, flushing or erythema are reported to occur in up to 90% of cases [30]. When cardiovascular symptoms occur simultaneously or shortly after skin manifestations, they are easily attributed to anaphylaxis. However, acute cardiac manifestations may appear as presenting signs of anaphylaxis; in these cases, the lack of skin symptoms makes it difficult to establish the correct diagnosis and to differentiate anaphylaxis from other clinical conditions such as myocardial ischemia.

The prevalence of cardiovascular involvement in the course of anaphylaxis was recently assessed by different studies. Worm *et al.* [31] reported data from a total of 2012 adults and pediatric patients who experienced anaphylactic reactions with severe pulmonary or cardiovascular symptoms. More than 70% of the reactions involved cardiovascular system, and older age was the factor most closely associated with an increased risk to develop circulatory symptoms; 38 patients (1.9%) developed cardiac arrest. A recent questionnaire-based survey conducted among emergency physicians in Germany found that up to 86% of reactions involved the cardiovascular system, with tachycardia and hypotension being the most common findings both in adults and in children, although hypotension was more common in adults (48.9% versus 28.6%) [32]. In this study, nine adult patients (3.5%), and none of the pediatric patients, experienced cardiovascular arrest. A retrospective survey conducted in a tertiary adult allergy unit in Turkey found that 41% of patients reported cardiovascular symptoms [33]. Moreover, in anaphylactic patients, cardiovascular symptoms, such as syncope and sweating, were found to be associated with an increased risk for the development of shock, particularly in elderly patients [34].

PREEXISTING CARDIOVASCULAR DISEASES AND FATAL ANAPHYLAXIS

World Allergy Organization (WAO) guidelines for the management of anaphylaxis recognize cardiovascular diseases as an important patient-related factor increasing the risk of severe or fatal anaphylactic episodes [35^{***}]. As mentioned above, the number of cardiac mast cells is increased in patients with ischemic heart disease and they are strategically located to control coronary blood flow, myocardial contractility and electrical functions of the heart. Therefore, it should not be surprising that in

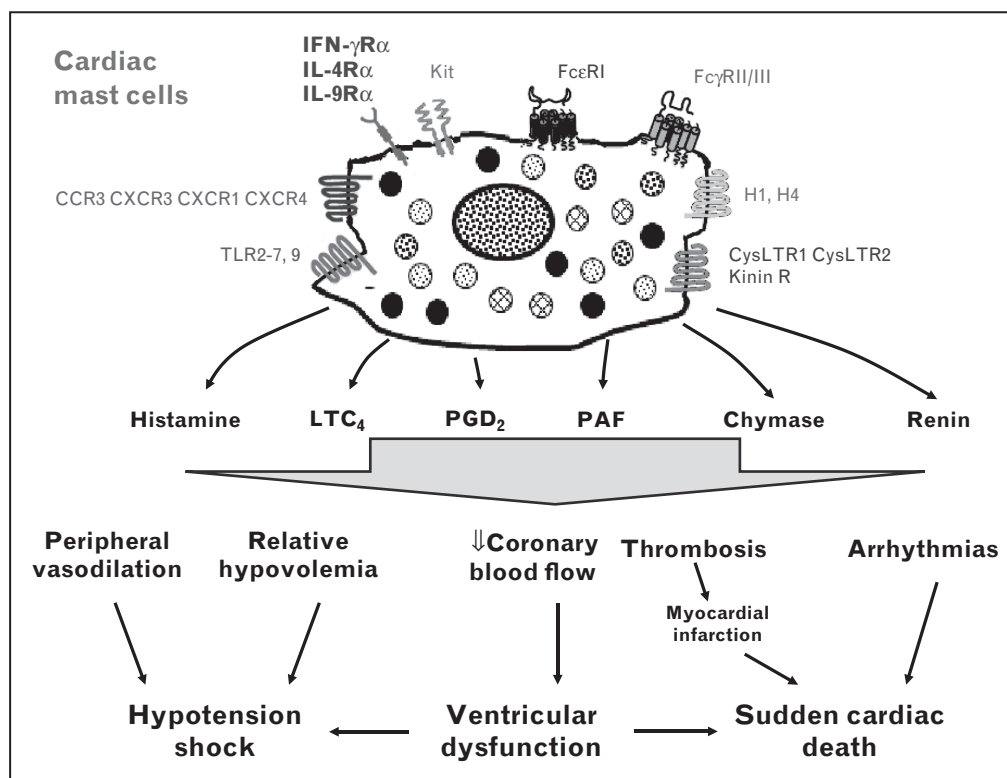


FIGURE 1. Cardiovascular effects of mast cell-derived mediators. Cardiac mast cells can be activated by various stimuli by the engagement of specific surface receptors. These include the high-affinity receptor for IgE (FcεRI) and IgG (Fcγ), the receptor for Stem Cell Factor (Kit), several Toll-like receptors (TLR) and receptors for cytokines and chemokines (CCR and CXCR). Mast cells also express receptors for mediators of allergic inflammation, such as histamine (H₁ and H₄) and leukotrienes (CysLTR). Activation of mast cells leads to the release of various mediators that exert multiple and redundant effects on the peripheral vascular system, responsible for hypotension and shock. In addition, mast cell-derived mediators act directly on the heart reducing coronary flow and myocardial contractility and inducing thrombosis and arrhythmias. These central (cardiac) responses concur with peripheral vasodilation in worsening the hemodynamic effects of anaphylaxis.

patients with preexisting coronary disease, anaphylaxis can be more severe or even fatal. A retrospective analysis that evaluated postmortem findings and the presence of comorbid diseases revealed that cardiovascular diseases were found in 16 out of 25 patients with documented fatal anaphylaxis. Notably, urticaria was reported in only one out of the 25 patients during the anaphylactic reaction [36]. A study in 29 fatalities after hymenoptera sting found that most of the patients had previous history or autopsy evidence of preexisting cardiovascular or lung disease. Autopsy done in 12 patients revealed coronary artery disease in 10 and other cardiomyopathies in seven patients [37]. In a group of 36 anaphylactic deaths caused by drug allergy, atherosclerotic coronary disease was reported in 15 patients (41.6%), including three cases with severe disease, three with moderate involvement and nine with mild involvement [38]. Together these data emphasize the tight relationship between an even unrecognized cardiac disease and fatal or near-fatal anaphylaxis.

ANAPHYLAXIS AND CARDIOVASCULAR DRUGS

Cardiovascular medications, such as β-blockers and angiotensin converting enzyme (ACE) inhibitors, are commonly prescribed drugs, and patients at risk of anaphylaxis who are receiving these drugs are frequently encountered by allergologists. Administration of β-blockers raises serious concerns that anaphylaxis in patients who are receiving these drugs can be more severe and refractory to treatment with epinephrine. ACE inhibitors directly interfere with metabolism of bradykinin, as ACE is a key enzyme responsible for its degradation. Moreover, ACE inhibitors and angiotensin-receptor blockers (ARBs) could potentially impair the endogenous compensatory response of RAS, which is crucial to maintain peripheral vasoconstriction in the case of severe hypotension [39]. The possibility that the use of antihypertensive drugs may influence the outcome of anaphylaxis has been recently addressed in a multicenter Emergency Department study. This study [40^a] revealed that use of antihypertensive

medications, including β -blockers, ACE inhibitors, ARBs, calcium channel blockers and diuretics, is associated with increased organ system involvement and increased odds of hospital admission, independently of age, sex, suspected trigger or pre-existing lung disease.

Because anaphylaxis is potentially occurring in patients undergoing allergen-specific immunotherapy, β -blockers are generally not recommended during this treatment [41,42]. However, evidence that β -blockers increase the rate or the risk of severe reactions during immunotherapy is relatively weak. Rueff and coworkers [43] performed a multicenter observational study in patients with hymenoptera venom allergy and systemic reaction to evaluate the predictors of the severity of reaction. In the multivariate analysis, ACE inhibitors, but not β -blockers, were identified as an independent predictor of severe reaction after sting ($P=0.019$, OR 2.269, 95% CI, 1.129–4.558). The same authors also evaluated the association of different parameters with the risk of a severe reaction during the build-up phase of venom immunotherapy (VIT) [44]. This study, in which 2.2% of patients were on β -blockers and 2.6% on ACE inhibitors, revealed that none of these drugs increased the risk of severe reactions. These data are in agreement with those from Mueller and Hepner that also reported no increased risk of systemic reactions during VIT in patients taking β -blockers [45,46]. Some case reports have been published regarding systemic reactions in patients taking ACE inhibitors during the course of VIT [47–49]. In some cases, reactions did not recur after ACE inhibitor discontinuation. However, data from a retrospective study by White and England [50] in 79 patients undergoing VIT of which 21% were on ACE inhibitors revealed that there is no significant association between ACE inhibitor use and increased frequency of systemic reactions.

UNIQUE ANAPHYLAXIS-ASSOCIATED CARDIAC SYNDROMES: KOUNIS SYNDROME AND TAKO-TSUBO CARDIOMYOPATHY

The heart being a potential target in anaphylaxis, it is not surprising that an acute coronary syndrome may occur as part of the reaction or as one of its predominant clinical features. Allergic reaction as a cause of acute coronary events was first described in 1950 and later known as Kounis syndrome in 1991 [51,52]. Kounis syndrome may present as either acute angina or myocardial infarction in the course of a type I hypersensitivity reaction. Clinical manifestations of Kounis syndrome can be highly variable ranging from subclinical reactions to severe coronary syndrome with ECG ischemic changes

and an increase in serum cardiac enzymes and troponine. The diagnosis is often difficult, particularly if other clinical signs of anaphylaxis, for example, urticaria, bronchoconstriction or hypotension, are absent and if clinical history is not focused on searching a possible trigger of allergic reaction. Three variants of Kounis syndrome have been described as follows: type I presents as coronary vasospasm in patients with normal coronary arteries; type II occurs in patients with preexisting quiescent, clinically silent atheromatous disease; type III refers to patients with thrombosis on a coronary artery stent in whom eosinophils and mast cells were isolated in the thrombus [53]. In the latter type, infiltration of thrombus by inflammatory cells, such as eosinophils, macrophages, plasma cells, T cells and mast cells, is a predominant feature [54]. All components of drug-eluting stents (metals, polymers and drugs) can trigger an allergic reaction and the consequent release of mediators, including PAF, cytokines and chemokines that can potentially induce thrombosis [55,56].

The most frequent triggers of Kounis syndrome include drugs, contrast media, latex, hymenoptera sting and food [57,58], but the number of causative agents is steadily increasing. For example, emerging food allergens such as *Anisakis* or new drugs such as losartan have recently been reported as a cause of Kounis syndrome [59,60]. A case of Kounis syndrome in a patient with E148Q mutation in familial Mediterranean fever gene was also reported [61].

Tako-tsubo cardiomyopathy, also called stress-induced cardiomyopathy, is a reversible left ventricular dysfunction associated with stress, including major surgery and partum. In some cases, Tako-tsubo has been associated with Kounis syndrome [62,63]. The release of endogenous catecholamines, associated with physical or emotional stress, plays an important role in determining the stress-induced cardiomyopathy. Cases of Tako-tsubo cardiomyopathy have been reported after administration of epinephrine during the treatment of anaphylaxis. Most of these cases were associated with either intravenous administration of epinephrine or very high doses of the drug given intramuscularly [64]. Most cases were resolved spontaneously within a few days and just a few patients required treatment for left ventricular failure. It should be also considered, however, that stress during an anaphylactic episode can be an additional factor to trigger Tako-tsubo cardiomyopathy [65].

MAST CELL-RELATED DISORDERS AND CARDIAC EMERGENCIES

Acute cardiac events are increasingly recognized as major clinical features or even presenting symptoms

of mast cell-related disorders, including mastocytosis and mast cell activation syndrome. Mastocytosis is a rare disease characterized by the proliferation and accumulation of mast cells in different organs. Symptoms and clinical findings of mastocytosis depend largely on the release of mediators from mast cells and tissue infiltration. Mast cell activation syndromes are clinically indistinguishable from mastocytosis, with severe mediator-related symptoms, in the absence of bone marrow criteria for systemic mastocytosis [66]. Reiter and colleagues [67] described a patient with systemic mastocytosis who experienced repeated cardiac arrests after mosquito bites, one of which resulted in spastic tetraplegia caused by anoxic encephalopathy. González-de-Olano *et al.* [68] reported a case series including 10 patients suffering from mast cell related disorders (systemic mastocytosis or mast cells activation syndrome) who experienced Kounis syndrome. In that series the triggers of the allergic reaction were drugs in four patients, food in two patients, hymenoptera sting in one patient, exercise in two patients, and both drug and hymenoptera sting in one patient. ECG showed ischemic changes in eight out of the 10 patients, whereas serum troponine was elevated in six cases [68].

Recently, we described three patients in whom a cardiac arrest or ventricular fibrillation was the first clinical manifestation of systemic mastocytosis [69]. Unique features of these cases were the absence of previous symptoms or clinical signs of mastocytosis, the lack of preexisting cardiovascular conditions and the electrical dysfunction as the dominant clinical presentation. Together these reports demonstrate the frequent involvement of the cardiovascular system in patients with underlying mast cell disorders and underscore the need for searching such conditions in all cases of unexplained cardiac event.

CONCLUSION

Mediators secreted by cardiac mast cells play a primary role in systemic and local manifestations of anaphylaxis. In this life-threatening reaction, molecules such as histamine, prostanoids and PAF exert major effects on coronary blood flow by influencing the tone of both large and small coronary arteries, reduce myocardial contractility and induce electrical dysfunction leading to arrhythmias and cardiac arrest. Cardiovascular diseases increase the rate of anaphylaxis and the risk of severe reactions primarily because they are associated with a dramatic increase in the number of cardiac mast cells at crucial sites such as the small intramural coronary arteries and atherosclerotic plaques in the

large epicardial vessels. Release of mast cell-derived mediators at these sites during anaphylaxis greatly enhances the possibility of acute myocardial ischemia because of vasospasm, plaque rupture and thrombosis. The role of cardiovascular drugs, such as β -blockers, ACE inhibitors and other antihypertensive agents, as aggravating factors of anaphylaxis remains unclear and deserves further studies. Similarly, the influence of acetylsalicylic acid and other antiplatelet agents largely used in cardiovascular prevention in the setting of anaphylaxis is completely unknown. Despite these areas of uncertainty, it is now clear that anaphylaxis is a dramatic condition that should be managed very carefully in patients with preexisting cardiovascular disorders. Both allergists and cardiologists should be aware of the complex interactions between anaphylaxis and cardiac diseases and should implement all preventive strategies to minimize the risks of this dangerous liaison.

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Conflicts of interest

There are no conflicts of interest.

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- of outstanding interest

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