

Kounis syndrome (allergic acute coronary syndrome): different views in allergologic and cardiologic literature

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Abstract The clinical picture of myocardial ischemia accompanying allergic reactions is defined in the cardiologic literature as Kounis syndrome (KS) or allergic angina/myocardial infarction. In PubMed, a search for “Kounis syndrome”, “allergic angina” or “allergic myocardial infarction” retrieves more than 100 results (among case reports, case series and reviews), most of which are published in cardiology/internal medicine/emergency medicine journals. In allergologic literature, heart involvement during anaphylactic reactions is well documented, but Kounis syndrome is hardly mentioned. Single case reports and small case series of angina triggered by allergic reactions have been reported for many years, and involvement of histamine and others mast cell mediators in the pathogenesis of coronary spasm has long been hypothesized, but the existence of an allergic acute coronary syndrome (ACS) is still questioned in the allergologic scientific community. Putative mechanisms of an allergic acute coronary syndrome include coronary spasm or heart tissue-resident mast cell activation (precipitating coronary spasm or inducing plaque rupture and coronary or stent thrombosis) due to systemic increase of allergic mediators, or heart tissue-resident mast cell activation by local stimuli.

Indeed, the pathogenic mechanism of an ACS after an allergic insult might be related to direct effects of mast cell mediators on the myocardium and the atherosclerotic plaque, or to exacerbation of preexisting disease by the hemodynamic stress of the acute allergic/anaphylactic reaction. Which of these mechanisms is most important is still unclear, and this review outlines current views in the cardiologic and allergologic literature.

Keywords Kounis syndrome · Allergic angina · Allergic myocardial infarction · Anaphylaxis

Introduction

Kounis syndrome (allergic angina) was defined in 1991 as “the coincidental occurrence of chest pain and allergic reactions accompanied by clinical and laboratory findings of classic angina pectoris caused by inflammatory mediators released during the allergic insult” [1]. In its actual conception, this syndrome comprehends the whole clinical spectrum of acute myocardial ischemia, from angina pectoris to acute myocardial infarction, which occurs in coincidence with an “allergic” (hypersensitivity, anaphylactic or anaphylactoid) reaction [2, 3].

As today, a PubMed search for “Kounis syndrome”, “allergic angina” or “allergic myocardial infarction” retrieves more than 100 results (among case reports, case series and reviews), most of which are published in cardiology/internal medicine/emergency medicine journals. To our knowledge, just a few papers have been published in immunologic or allergologic journals [2, 4, 5].

While in the cardiologic literature, allergic angina and allergic myocardial infarction are currently referred as “Kounis syndrome” (KS) [3], and are cited in major

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cardiovascular textbooks [6] as a new cause of coronary artery spasm, in allergologic literature, KS is hardly mentioned. In a review, Brown emphasizes that although mediators released by mast cells may cause significant vasospasm and plaque ulceration, triggering angina or infarction, reports about this phenomenon are inherently selective, and may represent chance occurrences [7].

Will these parallel lines ever meet?

Allergic angina and allergic myocardial infarction—the cardiologist's view

The typical patient with KS is a middle-aged man, who develops allergic symptoms and myocardial ischemia after the exposure to a potential allergenic trigger [8]. Nevertheless, KS has also been recently described in children [9]. Diagnosis of acute myocardial ischemia should be based upon the usual clinical, laboratory and electrocardiographic findings. Associated signs and symptoms such as urticaria, angioedema and dyspnea may provide a clue for diagnosis [8].

Initial descriptions of this syndrome focused on patients with “angiographically” normal coronary arteries, in which acute release of allergic mediators, such as histamine or leukotrienes, could induce a vasospastic angina (type I variant KS) [10]. In these patients, allergic mediators usually responsible for vasodilatation may induce coronary spasm in the presence of endothelial dysfunction [10]. The clinical course can vary from artery spasm without increase of cardiac enzymes and troponins, to acute myocardial infarction [2]. In every patient with myocardial ischemia, an absence of coronary obstruction on angiography should raise the possibility of an “allergic” mechanism, and activate a thorough history re-evaluation, in search of a putative allergic trigger.

In type II variant of the KS, quiescent atherosclerotic plaques may rupture, and coronary thrombosis may develop as a result of the acute release of inflammatory

mediators after an allergic insult [10]. Therefore, acute allergic reactions followed by acute myocardial infarction with angiographic evidence of coronary artery disease constitute the prototypical type II variant of KS [2, 3, 11, 12].

More recently, a type III variant of the syndrome has been proposed [13], after an association between KS and drug-eluting stent thrombosis has been postulated [12, 14, 15]. The type III variant would include patients with stent thrombosis in whom thrombus harvesting and staining with hematoxylin–eosin and Giemsa shows the presence of eosinophils and mast cells, respectively, in the pathology specimens [16]. As mast cells are abundant in an atherosclerotic lesion [17, 18], their activation (also involving other inflammatory cells, including eosinophils [19, 20], macrophages and lymphocytes) and the release of platelet activating factors and of various other pro-inflammatory mediators such as cytokines and chemokines, has been implied in the phenomenon of drug-eluting stent thrombosis [15]. Although the pathogenesis of drug-eluting stent thrombosis is multifactorial, and has not been fully elucidated, it has been proposed that allergic reactions to stent components (either nickel strut, polymer or impregnated drug) may play a role in this pathological entity [2, 14].

Table 1 summarizes the three clinical variants of Kounis syndrome [21].

On electrocardiography, ST elevations in anterior and inferior leads have been the most reported findings in patients diagnosed with KS, although the ECG may be normal, or merely show nonspecific ST-T wave changes [2].

The usual laboratory workup, including cardiac enzymes and troponins is needed to assess the diagnosis. Evaluation for other causes of coronary syndromes, especially in younger patients, is advisable: in this case, laboratory evaluation should search for thrombophilic conditions such as the presence of antiphospholipid antibodies and lupus anticoagulant, increased lipoprotein A levels, deficiency of protein C, protein S or antithrombin III, alteration of

Table 1 Types of Kounis syndrome

Clinical variant	Pathogenic mechanism
Type I: coronary spasm	Normal or nearly normal coronary arteries without predisposing factors for coronary artery disease in whom the acute release of inflammatory mediator can induce either coronary artery spasm without increase of cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins
Type II: coronary spasm/thrombosis in atheromatous disease	Culprit but quiescent preexisting atheromatous disease in whom the acute release of inflammatory mediators can induce either coronary artery spasm with normal cardiac enzymes and troponins or coronary artery spasm together with plaque erosion or rupture manifesting as acute myocardial infarction
Type III: drug-eluting stent thrombosis	Coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin–eosin and Giemsa demonstrate the presence of eosinophils and mast cells, respectively

plasminogen activator and inhibitor activity, dysfibrinogenemia. If a differential diagnosis with myopericarditis is needed, serologic tests for viral infections are necessary [2].

Transthoracic echocardiography may be useful to differentiate KS from other causes of chest pain, such as pericarditis or aortic dissection; most common findings are represented by segmental wall motion abnormalities, which subside in a few days or weeks after the acute phase of disease. Coronary angiography is usually needed to assess coronary anatomy, and for differential diagnosis [2].

Heart involvement in anaphylaxis—the allergist's view

Anaphylaxis is a severe, life-threatening, generalized or systemic hypersensitivity reaction [22], in which mast cells and basophils play a major role through the release of mediators (Fig. 1) [23, 24], such as histamine, leukotrienes and others [25].

Patients suffering from anaphylaxis may present with cardiovascular symptoms, including hypotension, cardiovascular collapse, cardiac dysrhythmia and chest pain, likely caused by massive mediators released by mast cells, which are present in heart tissues [7, 25–27].

Cardiovascular symptoms are highly important in the current, operative, definition of anaphylaxis, since reduced blood pressure is the only clinical finding that alone allows diagnosis of anaphylaxis after exposure to a known allergen (Table 2) [23].

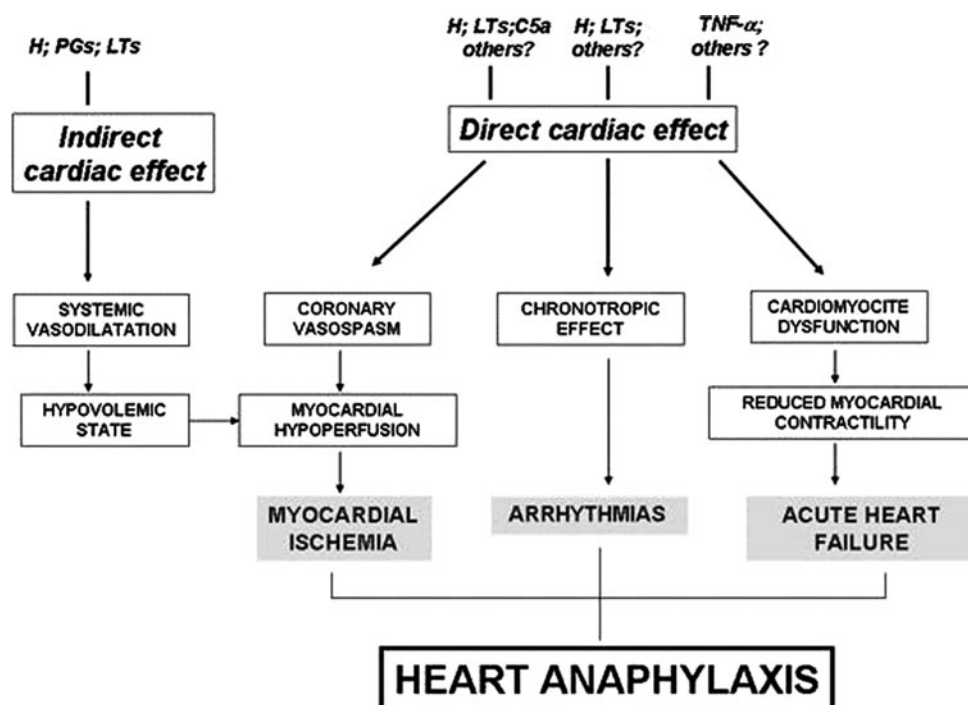
Table 2 NIH definition of anaphylaxis (one of three clinical scenarios) [23]

Scenario 1	The acute onset of a reaction (minutes–hours) with involvement of the skin, mucosal tissue or both and at least one of the following:	Respiratory compromise Reduced blood pressure or symptoms of end-organ dysfunction
Scenario 2	Two or more of the following that occur rapidly after exposure to a likely allergen for that patient:	Involvement of the skin/mucosal tissue Respiratory compromise Reduced blood pressure or associated symptoms Persistent gastrointestinal symptoms
Scenario 3	Reduced blood pressure after the exposure to a known allergen	

The same panel of experts that proposes the previous definition recognizes that anaphylaxis can present as an acute cardiac event [23]. Even if cutaneous, mucosal or respiratory symptoms are often needed to establish a firm diagnosis of anaphylaxis [23], it has to be noted that a study reports that these are not present in a large part of a group of 25 patients who died of anaphylaxis [28]. Finally, it is known that the heart and the circulatory system are predominant shock organs in humans, from anaphylaxis of whatever cause [29].

From all this, we can draw the conclusion that most of the allergic reactions with heart involvement easily converge into the definition of anaphylaxis, and that heart

Fig. 1 Mediators of acute allergic and non-allergic hypersensitivity reactions and heart anaphylaxis (from [25] with permission)



involvement is a common finding in anaphylaxis. On the other hand, cardiovascular symptoms are rarely seen during mild-to-moderate (non-anaphylactic) allergic reactions.

Why then is the existence of an allergic acute coronary syndrome (ACS) still questioned in the allergologic scientific community?

Effects of chemical mediators of anaphylaxis are reviewed by Kemp and Lockey [29]. These mediators appear to affect the myocardium directly [30, 31]. Histamine, through its H₁ receptors, mediates coronary artery vasoconstriction, and increases vascular permeability, whereas activation of H₂ receptors increases atrial and ventricular contractile forces, heart rate, and coronary artery vasodilatation. The interaction of H₁ and H₂ receptor stimulation appears to mediate decreased diastolic pressure and increased pulse pressure [32]. Animal studies suggest a possible modulatory role for H₃ receptors [33]. Histamine can also activate platelets and potentiates the aggregatory response of other agonists including adrenaline, 5-hydroxytryptamine, and thrombin; it modulates the activity of inflammatory cells such as neutrophils, monocytes, and eosinophils. Moreover, histamine induces pro-inflammatory cytokine production from endothelial cells, up-regulates P-selectin on the endothelial cell surface, and induces intimal thickening in a mouse model of thrombosis [3].

Platelet-activating factor also decreases coronary blood flow, delays atrioventricular conduction, and has depressor effects on the heart [30].

Moreover, increased vascular permeability during anaphylaxis can result in a transfer of 50% of the intravascular fluid into the extravascular space within 10 min [29]. This shift in effective blood volume activates the renin–angiotensin–aldosterone system, and causes compensatory catecholamine release, both of which have variable clinical effects, from maximal vasoconstriction to decreased systemic vascular resistance [29].

As already stated, mast cells are abundant in heart tissue [7, 26, 27], they accumulate at sites of coronary plaques [17, 18], and may contribute to coronary artery thrombosis [34]. Histamine released from mast cells may also promote plaque disruption by increasing the arterial hemodynamic stress on the plaque, inducing vasospasm. [35]. Mast cells may also be (co)activated upon binding to extracellular matrix molecules, thereby releasing a variety of cytokines into its environment [36, 37]. In particular, mast cell proteases—tryptase and chymase—are able to activate matrix metalloproteinases (MMPs) leading to degradation of collagen and elastin [38–40], consequently resulting in further destabilization of the plaque. Increased numbers of activated mast cells have been identified in particular in the adventitia of vulnerable and ruptured lesions in patients with myocardial infarction, and more importantly, their

number is found to correlate with the incidence of plaque rupture and erosion [41–43].

Because a number of stimuli can trigger mast cell degranulation, IgE-mediated allergic reactions foremost, it is conceivable that any allergic reaction could potentially facilitate plaque disruption. Coronary microvascular spasm has been demonstrated in subjects with vasospastic angina [44], and allergic mediators might have a role in this mechanism as well.

Single case reports and small case series of angina triggered by allergic reactions have been reported for many years, and involvement of histamine and other mast cell mediators in the pathogenesis of coronary spasm has long been hypothesized [10], but retrospective studies of that period [45], and some subsequent studies aiming at demonstration of a systemic increase of mast cell activity and therefore of circulating levels of mast cell mediators during ACS [46], fail to show any significant result.

Tsutsui and co-workers [45] analyzed retrospectively just a small series of patient with variant angina, while van Haelst and co-workers [46], instead, tried to demonstrate a systemic elevation of mast cell mediators, but their increase is either too brief or too small to be detected in the peripheral blood during an ACS.

Conversely, Cuculo et al. [47] report that tryptase levels increase in the peripheral blood of patients undergoing a spontaneous episode of myocardial ischemia, but not during an ergonovine-induced coronary spasm, thus suggesting that mast cell activation in ACS is a primary event, and not a result of coronary spasm itself. In this study, tryptase levels were measured after 0, 5, 15 and 60 min since the onset of chest pain or detection of ECG changes.

In the study by Filipiak et al. [48], serum tryptase elevation was detected in patients undergoing ACS with respect to controls, with the highest concentrations found in patients with ST-segment depression both in the acute phase and at follow-up. This finding suggests that serum tryptase levels may differentiate patients with distinct types of ACS [48].

From the allergist's point of view, it can be said that anaphylaxis is clinically associated with myocardial ischemia and other cardiovascular abnormalities. Even non-anaphylactic allergic reactions have been related to ACS, and are theoretically capable of inducing such pathogenic mechanisms, via activation of heart tissue-resident mast cells and degranulation of their mediators. Whether this could be related to direct effects of mast cell mediators on the myocardium and the atherosclerotic plaque, or to exacerbation of a preexisting disease by the hemodynamic stress of the acute allergic/anaphylactic reaction is still unclear.

Further studies are needed to address this question appropriately. Putative mechanisms of an “allergic acute

coronary syndrome” should include: (a) coronary spasm or heart tissue-resident mast cell activation (precipitating coronary spasm or inducing plaque rupture and coronary or stent thrombosis) due to systemic increase of allergic mediators during an allergic/anaphylactic reaction; and (b) coronary spasm, plaque rupture and coronary or stent thrombosis, due to heart tissue-resident mast cell activation by local stimuli after an allergic reaction (such as hypoxemia or ischemia due to reduced blood pressure).

Kounis syndrome—a concise review of literature

More than 50 years has passed since the first report of an acute myocardial infarction after an allergic reaction [49]. At present there is an extensive literature made up of many case reports and small case series, such as the one recently published in this Journal [50]. There is a clear record that acute coronary syndromes are continuously reported after either anaphylactic or non-anaphylactic allergic reactions.

There are several allergic triggers, and even nonallergic direct mast cell activators that have been reported as capable of inducing KS; these encompass drugs (such as antibiotics, analgesics, anesthetics and contrast media), environmental stimuli (such as insect sting, jellyfish sting, viper venom poisoning, poison ivy contact) and foods (shellfish, kiwi) [3].

Epidemiologic data about allergic reactions are very difficult to collect, and anaphylaxis has been defined “a not reportable disease”, since its morbidity and mortality are underestimated [29]. Anyway, cases of KS have been reported worldwide, in patients aged 9- to 90-year old [2]. It is considered a rare disease, but its real prevalence and incidence are completely unknown, since many physicians are unaware of the diagnosis and no prospective trials currently exist.

A recent review about KS following beta-lactam antibiotic use, although the number of published cases is limited, note that this syndrome seems to have a lower mortality and a better short-term prognosis than the usual ACS [51], as no mortality has ever been reported. The prognosis of patients with KS is very good beyond the acute phase, with the left ventricle function normalizing over 3 days to several weeks [2]. This data about KS related to beta-lactam allergy, however, may represent an underreporting bias given that large-scale reviews of adverse drug reactions have found beta-lactams to be the most frequent culprit drugs [52] and that a significant mortality can be attributed to these adverse reactions [53].

Currently, treatment guidelines for the patients with KS have not been established, and most of the information about the treatment of this syndrome comes from individual case reports or case series. In KS, two different aspects

of disease need to be treated: the acute coronary syndrome and the allergic reaction. Treatment of the allergic reaction alone can be sufficient in case of the type I variant, while concomitant treatment of ACS is mandatory in the type II variant [2]. Treatment options for KS have been recently reviewed by Cevik et al. [54].

Conclusions

Direct and indirect evidence about the role of “allergic” mediators in some cases of ACS is increasing. Many clinical observations have also been published (case reports or case series), but conclusive data are still lacking.

Cardiologists are used to reading about KS in major cardiovascular textbooks, as a new cause of coronary artery spasm, whereas allergic angina and allergic myocardial infarction are not usually considered in the allergologic literature.

In our view, the occurrence of ACS after an allergic reaction in patients (and even in children) with intact coronary arteries (type I variant KS) is a strong argument in favor of a direct role of allergic mediators, whereas the more complex pathogenesis in patients with preexisting coronary artery disease or drug-eluting stent thrombosis (type II and type III KS) still needs to be fully clarified. In these patients, pathogenic mechanisms may be related to the direct effects of mast cell mediators on the myocardium and the atherosclerotic plaque, or to exacerbation of pre-existing disease by the hemodynamic stress induced by the acute allergic/anaphylactic reaction.

Conflict of interest None.

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