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Editorial

Anaphylaxis affects primarily the heart and coronary arteries: Implications of Kounis syndrome

Nicholas G. Kounis [1,*] **and Ioanna Koniari** [2]

[1]Department of Cardiology, University of Patras Medical School, Patras, Greece
[2]Department of Electrophysiology, Queen Elizabeth Hospital, Birmingham, United Kingdom

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***Correspondence to**
Nicholas G. Kounis
Department of Cardiology, University of Patras Medical School, Rion, 7 Aratou Street, Queen Olgas Square, Patras 26221, Greece.
Tel: +302610279579
Fax: +302610279579
E-mail: ngkounis@otenet.gr

ORCID iDs
Nicholas G. Kounis
https://orcid.org/0000-0002-9751-6710

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Clinical and experimental studies have shown that the heart and especially the coronary arteries constitute the primary targets of anaphylactic inflammatory mediators [1] which could induce coronary injury with increased cardiac troponin and mast cell tryptase levels. The elevated tryptase levels document anaphylactic reaction while the increased troponin levels combined with ischemic changes document acute myocardial injury. Whereas other studies have shown that tryptase is elevated in acute coronary events of nonanaphylactic etiology [2] and that troponin could also increase in allergic reactions [3]. This confirms our findings of a common pathway for coronary events in both allergic and nonallergic reactions [4].

Beyond anaphylaxis, the main concept lies to myocardial damage and ventricular dysfunction, which can lead to shock and cardiovascular collapse. It is commonly believed that the depression of cardiac output due to coronary hypoperfusion from systemic vasodilation associated with leakage of plasma and volume loss due to increased vascular permeability, and the following reduced venous return, constitute the main causes of cardiovascular collapse encountered in anaphylactic shock. Indeed, during anaphylactic shock circulating blood volume may decrease by as much as 35% within 10 minutes due to transfer of intravascular fluid to extravascular space [5].

In the very important paper published *Asian Pacific Allergy* [6], the authors, showed, for the first time, that cardiac dysfunction may develop during anaphylactic reaction independent of the severity of reaction and with suitable treatment may resolve after recovery from anaphylaxis. They used the QLAB-CMQ software program of Speckle tracking echocardiography and measured the global longitudinal strain (GLS) via apical chambers (4 chambers, 3 chambers, 2 chambers) through at least 4 consecutive cardiac cycles. They found that the GLS value was lower shortly after the anaphylaxis than those measured 6 weeks later in 50% of the patients and was also lower during the reaction in the anaphylaxis group than in the urticaria. Furthermore, the lower GLS has been recently associated with a higher long-term risk of cardiovascular morbidity and mortality in a low-risk general population [7, 8].

This report raises important issues as far as the heart and especially the coronary arteries acting as primary targets of anaphylaxis is concerned. It comes to corroborate the following experimental and clinical findings that seem to have clinical, pathophysiologic, and therapeutic repercussions.

Indeed, experiments, with ovalbumin sensitized guinea pigs anaphylaxis model, have shown that within 3-minute post ovalbumin administration the followings cardiac events have occured [9]: (1) cardiac output decrease by 90%; (2) left ventricular end diastolic pressure significant increase by 35%, indicating pump failure; (3) arterial blood pressure increases significantly by 35% and starts declining steadily after 4 minutes; (4) concurrent electrocardiographic changes reveal signs of acute myocardial ischemia.

The conclusion was: "the idea that the registered anaphylactic damage might be due to peripheral vasodilatation can be definitely excluded."

In a recent experimental model with anaphylaxis, that was induced by ovalbumin antigen injection into open-chest of artificially ventilated sensitized mice the followings were found [10]: (1) Aortic blood flow and mean arterial pressure progressively decreased after an initial transient increase. (2) Total peripheral resistance reduction was not observed while pulmonary artery pressure showed initially a transient increase up to 18.5±0.5 mmHg along with pulmonary vascular resistance increment. (3) Aortic blood flow and the mean arterial pressure decrease were attenuated by pretreatment with either a platelet-activating factor receptor antagonist, or by histamine H_1 receptor antagonist, -diphenhydramine-, and further were abolished by their combination.

The authors again concluded that mice anaphylactic hypotension could be only attributed to cardiac output reduction via platelet activating factor and histamine actions and not to vasodilation.

In a recent clinical study [3] of 31 patients admitted to the Emergency Department suffering from anaphylaxis, angioedema, urticaria and urticaria angioedema it was found, for the first time, a significantly increase of cardiac troponin I concentration compared to 125 healthy controls. In the subgroup of anaphylaxis, the cardiac troponin I levels were higher than those of patients with milder allergic reactions. The authors suggested systematic troponin measurement in patients with acute allergic reactions in order to detect and treat potential myocardial injury. Indeed, these findings might have profound clinical, therapeutic and pathophysiologic implications as far as anaphylaxis, myocardial injury and Kounis anaphylaxis-associated acute coronary syndrome are concerned.

In another recent study [11] concerning 300 patients with anaphylactic reactions, who were assessed by electrocardiography, echocardiography and troponin measurements, myocardial injury was observed in 22 patients (7.3%). Cardiomyopathies, such as Kounis syndrome and Takotsubo cardiomyopathy were present in patients with myocardial injury. No mortality was observed in myocardial injury group, but there were 9 patients with documented cardiac arrest. One patient died due to multiple organ failure.

The authors concluded that further prospective studies are required to investigate the prognosis of cardiac injury in patients with anaphylaxis.

Furthermore, in an atopic patient allergic to milk protein, with eczema and bronchial asthma, anaphylactic reaction induced hemodynamic collapse and myocardial stunning leading to reduced cardiac output. The condition did not respond to intravenous Ringer acetate, antiallergic treatment with adrenaline and corticosteroids. Whereas her condition was complicated by pulmonary edema and decompensated heart failure, the patient responded satisfactorily and recovered only after myocardial infarction protocol treatment [12].

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All above together with the new findings of Demir et al. [6] show that anaphylaxis affects the heart and especially the coronary arteries inducing cardiac dysfunction independent of the severity of reaction and with suitable treatment may resolve after recovery from anaphylaxis. In anaphylaxis myocardial involvement due to vasospasm-induced coronary blood flow reduction manifesting as Kounis syndrome should be always considered [1]. Clinically, combined treatment targeting the primary cause of anaphylaxis together with protection of cardiac tissue seems to be of paramount importance.

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