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Commentary on: Feltracco P, Barbieri S, Galligioni H, Pasin L, Gaudio RM, Tommasi A, et al. A fatal case of anaphylactic shock during paragliding. J Forensic Sci 2012; doi: 10.1111/j.1556-4029.2012.02187.x [Epub ahead of print].

Sir,

Kounis syndrome (1) is the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and includes anaphylactic or anaphylactoid and allergic or hypersensitivity insults. It is caused by preformed and newly synthesized inflammatory mediators released during the anaphylactic process (2).

Three variants of Kounis syndrome have been described so far (3): In type I variant, coronary spasm, in normal or nearly normal coronary arteries, associated with anaphylactic reaction can progress to myocardial infarction. In type II variant, culprit but quiescent pre-existing atheromatous disease combined with anaphylactic reaction can result in acute myocardial infarction. In type III variant, hypersensitivity to any implanted intracoronary stent components can result in devastating intrastent thrombosis.

In the very important paper published recently in the *Journal of Forensic Sciences* (4), a 45-year-old paraglider, with a medical history of serious allergies including severe pruritus, urticaria, bronchospasm, and signs of shock, after a bee/wasp sting, started abruptly to spin and fall while gliding. He was found afterward dead on the ground with a protruding and swollen tongue and a dead bee over the tongue, underneath the palate.

Although postmortem serum IgE and tryptase levels were not measured and no bronchial obstruction, pulmonary emboli, coronary artery disease, or specific pulmonary edema was detected, the authors concluded that his death was attributable to anaphylactic shock on clinical grounds.

An important question that arises in this case is whether coronary spasm leading to Kounis syndrome and not the ensuing hypoperfusion of the heart owing to vasodilation and shock, were the cause of the anaphylactic death.

Indeed, experimental and clinical studies indicate that the human heart can be the primary site and the target of anaphylaxis, resulting in the development of Kounis syndrome (1).

So far, it is generally believed that during severe anaphylaxis and prior to an anaphylactic death, systemic vasodilation, reduced venous return, leakage of plasma and volume loss owing to increased vascular permeability lead to depression of cardiac output and contribute to coronary hypoperfusion with subsequent myocardial damage. Indeed, during severe acute anaphylactic reaction, circulating blood volume may decrease by as much as 35% within 10 min because of transfer of intravascular fluid to extravascular space, and severe vasodilation that resists to epinephrine and responds only to other potent vasoconstrictors has been reported (5–7). This effective shift of fluid volume is countered by compensatory vasopressor mechanisms involving the release of epinephrine and norepinephrine as well as the activation of angiotensin system (8,9). The ensuing increase in catecholamines might produce varied effects. Some patients during acute anaphylactic episodes experience maximum peripheral vasoconstriction (10), whereas others have decreased systemic vascular resistance (8). These variable effects of internal compensatory mechanisms might explain why epinephrine injections sometimes fail to help acute and severe anaphylaxis. Furthermore, the endogenous catecholamine release, which can be enhanced by therapeutic administration, can have an adverse effect in myocardium, including ischemic chest pain and electrocardiographic changes in the absence of diseased coronary arteries (11,12).

In experimental anaphylaxis with ovalbumin-sensitized guinea pigs (13), it was shown that within 3 min after the antigen administration, cardiac indices were changed as follows:

- cardiac output decreased by 90%,
- left ventricular end diastolic pressure increased significantly by 35%, indicating pump failure,
- arterial blood pressure increased significantly by 35% and blood pressure started declining steadily after 4 min, and
- concurrently, electrocardiographic changes showed signs of acute myocardial ischemia.

The authors of these experiments concluded that "the idea that the registered anaphylactic damage might be due to peripheral vasodilation can be definitely excluded. In addition, the rapid increase in left ventricular end diastolic pressure suggests that decreased venous return and volume loss owing to an increase of vascular permeability are unlikely to be the primary causes of the documented depression of cardiac output and blood pressure."

In another experiment (14), the anaphylactic cardiac damage was dissociated temporarily into two sets of events: an initial primary cardiac reaction caused by intracardiac release of histamine and a subsequent cardiovascular reaction secondary to systemic release of mediators. Other studies (15), with isolated guinea pig hearts undergoing anaphylaxis following intra-aortic injection of antigen, showed an abrupt heart rate increase, reaching the peak within 2 min, a transient increase in ventricular contractile force followed by prolonged decrease, and a prompt and prolonged decrease in coronary blood flow.

In a clinical study (16) of five patients with spontaneous angina—four of whom had significant (>70% stenosis) coronary artery disease and one with normal coronaries after infusion of histamine, with pretreatment with cimetidine to antagonize H2 receptors—two patients (40%) developed angina during histamine infusion, accompanied by ST-T elevation, decreased coronary blood flow, and increased coronary vascular resistance, but with no significant changes in the mean arterial blood pressure. In one of these two patients, coronary arterial spasm involving the circumflex coronary artery was angiographically demonstrated during histamine-induced angina, indicating that stimulation of the H1 receptor induces a reduction in coronary blood flow either from vasodilation of small coronary resistance vessels or from stimulation of vasoconstricting H1 receptors of large epicardial coronary arteries.

All above clinical and experimental studies indicate that during anaphylaxis, the heart and especially the coronary arteries are the primary target of anaphylaxis and should be always examined in any postmortem screening. The ensuing anaphylactic death is most likely to be due to coronary hypersensitivity, particularly due to Kounis syndrome.

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