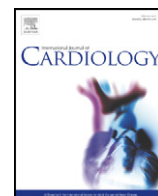




Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Editorial

Adrenaline administration for anaphylaxis and the risk of takotsubo and Kounis syndrome

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ARTICLE INFO

Article history:

Received 28 October 2012

Received in revised form 11 November 2012

Accepted 25 December 2012

Available online xxxx

Keywords:

Adrenaline

Allergy

Anaphylaxis

Hypersensitivity

Kounis syndrome

Takotsubo syndrome

Exogenous adrenaline administration is a life saving procedure, but it has been shown to promote platelet activation via specific receptors found on the platelet surface [1], to induce platelet aggregation by increasing platelet production of thromboxane B2 and heightening platelet sensitivity to ADP [2] and to promote thrombin induced binding of platelets to fibrinogen [3].

In the very interesting report published in this Journal [4] the authors described a 49-year-old atopic female nurse with previous atopic eczema, asthma and allergy to milk protein who suffered an anaphylactic reaction and despite repeated adrenaline injections she developed contemporarily takotsubo and anaphylactic Kounis syndrome. Troponin T was raised, electrocardiogram showed non-ST elevation myocardial infarction, chest X-ray showed pulmonary congestion, ejection fraction was reduced to 45%, transthoracic echocardiography showed severe hypokinesia of all the basal segments of the left ventricle with normal mid and apical segments while ventriculography revealed basal and mid-left ventricular and apical hypokinesia. The medications the patient received during the course of her illness were: intravenous adrenaline 0.1 mg thrice, fluid challenge with 1000 ml of Ringer's acetate, 125 mg of methylprednisolone intravenously and several inhalations of cholinergic ipratropium bromide and beta agonist fenoterol

hydrobromide but without any response. Aspirin and ACE-inhibitor were also given but were stopped due to symptomatic hypotension. She recovered gradually within one week.

This report raises several important issues on treatment of anaphylaxis and pathophysiology of takotsubo and Kounis syndrome.

First, it is generally believed that, during anaphylactic episodes, systemic vasodilatation, reduced venous return, leakage of plasma and volume loss due to increased vascular permeability, and the ensuing depression of cardiac output contribute to coronary hypoperfusion with subsequent myocardial damage. However, in the above report [1] the hemodynamic status was unresponsive to intravenous administration of fluids such as Ringer's acetate and prednisolone. Following this, the authors correctly commented, that hemodynamic disturbance was most probably due to myocardial stunning and creation of takotsubo appearance leading to reduced cardiac output rather than due to fluid extravasation. This comes to corroborate our view that the human heart can be the primary site and target of anaphylaxis [5] resulting in the development of Kounis syndrome [6]. Indeed, in experimental anaphylaxis with ovalbumin sensitized guinea pigs [7] it was shown that soon after the antigen administration electrocardiography uniformly showed signs of acute myocardial ischemia, decreased cardiac output by 90%, and significantly increased arterial blood pressure by 35% as did the left ventricular end diastolic pressure indicating pump failure. The blood pressure started declining steadily after 4 min. The authors of this paper 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 due 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 study [8] with isolated guinea pig hearts undergoing anaphylaxis following intra-aortic injection of antigen, a prompt and prolonged decrease in coronary blood flow, an abrupt heart rate increase reaching the peak within 2 min, and a transient increase in ventricular contractile force followed by a prolonged decrease of such were observed. These findings have corroborated the findings of a previous report [9] according to which the anaphylactic cardiac damage can be 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.

Second, the described atopic lady received ipratropium bromide and fenoterol inhalations, as well as repeated adrenaline injections

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which occasionally can induce myocardial ischemia [10,11]. She also took aspirin and an ACE-inhibitor which were stopped due to worsening of hypotension. There are some instances where these drugs can act as antigens, and worsen anaphylactic reaction. For example, a therapeutic dilemma arises in the sulfite allergic patient [12]. Every commercially available preparation of adrenaline contains, as preservative, according to Drug Facts and Comparisons (a standard pharmacy reference published by Wolters Kluwer and updated monthly) sodium metabisulfite. Sodium metabisulfite is commonly used as an antioxidant in food and pharmaceutical industries. Anaphylactic shock has been reported during epidural anesthesia for Caesarian section in which the responsible agent was metabisulfite an additive agent of adrenaline containing local anesthetic [13]. Only few physicians are aware of this treacherous association. Fortunately, nowadays, free sulfite adrenaline is commercially available for use in sulfite sensitive patients (American Regent Inc, USA) [14]. On the other hand, the involvement of all these drugs can act synergistically and cause IgE-mediated mast cell degranulation. It is known that anaphylaxis is initiated by allergens cross-bridging their corresponding, receptor-bound, immunoglobulin IgE or IgG antibodies on the surface of the mast cells or basophils. A total of 1000 bridges are necessary to trigger the cell out of a maximum number of some 500,000–1,000,000 IgE molecules on the cell surface. It might be possible to accumulate the critical number of bridges by more than one noncross-reactive antigen and its corresponding IgE which means that these bridges can be made by antigens of different specificities as in this case [15]. It looks likely, that the more antigens a patient with anaphylaxis is exposed to, the easier and quicker mast cell degranulation occurs.

Third, takotsubo syndrome or apical ballooning syndrome, named from a Japanese pot for catching octopus-like appearance of the heart on left ventriculography, is a clinical condition affecting mainly women, associated with emotional distress, resembling acute myocardial infarction, but with normal coronary arteries and transient left ventricular dysfunction. Many questions regarding etiology, pathophysiology and treatment remain unanswered. The release of various cytokines has been incriminated to induce it [16]. Adrenaline is considered to be the drug of choice for anaphylactic shock, but excess doses might contribute to coronary spasm and transient takotsubo syndrome through direct myocardial stunning. Mediators released during anaphylaxis may initiate coronary spasm and takotsubo syndrome [17].

In anaphylaxis, compensatory catecholamine is released by the renin-angiotensin-aldosterone system and histamine stimulates the release of catecholamine by direct action on the adrenal medullary cells. Catecholamine increase, with excessive activation of cardiac catecholamine receptors in the left ventricle, plays a major role in the pathophysiology of stress-induced cardiomyopathy [18]. In addition to this phenomenon, administration of catecholamines, such as adrenaline and noradrenaline, for hemodynamic support of anaphylactic shock would also increase the plasma catecholamine level. Catecholamine increase, in patients with angina, renders blood platelets more sensitive and more prone to aggregation and thrombosis. Indeed, adrenaline administration has already induced acute drug-eluting stent thrombosis [19]. Since, anaphylactic reaction can also induce takotsubo syndrome, measurement of anaphylactic inflammatory mediators such as histamine, chymase, leukotrienes, thromboxane and platelet activating factor or the use of corticosteroids or mast cell stabilizers for prevention and treatment may shed light on its etiology and pathophysiology.

Adrenaline, takotsubo, anaphylaxis, and Kounis syndrome (ATAK) seem to constitute a challenging contemporary complex [20]. We urge the research community to “attack” in order to elucidate its etiology and pathophysiology and to apply the proper preventive and therapeutic measures.

Acknowledgments

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [21].

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