

The heart seems to be the primary site and the target of anaphylaxis resulting in the development of Kounis syndrome

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In a very important paper published in this journal [1], two patients suffering from severe anaphylaxis developed electrocardiographic ST segment elevation associated with prominent cardiovascular symptoms. The first patient's urticaria was accompanied by chest pain, tachycardia and hypotension, and skin prick tests were positive for beef, pork and milk. The second patient's urticaria was developed intra-operatively, and was accompanied by hypotension culminating in ventricular tachycardia and ventricular fibrillation necessitating cardiac defibrillation. This patient had received propofol, sevoflurane, fentanyl, atracarium and epinephrine and had positive skin prick tests to atracarium and latex.

All the above symptoms are characteristic for type I variant of Kounis syndrome for the first patient, and type II variant of Kounis syndrome for the second patient. Kounis syndrome is defined [2] as the concurrence of acute coronary syndromes with conditions associated with mast cell degranulation and other interacting and interrelated inflammatory cells such as T lymphocytes and macrophages. It is caused by inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet-activating factor, and a variety of cytokines and chemokines released during the activation process. It seems possible that the first patient suffered a type I variant of Kounis syndrome, which is seen in patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery 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 progressing to acute myocardial infarction with raised cardiac enzymes and troponins.

On the other hand, type II variant of Kounis syndrome includes patients with culprit but quiescent preexisting atherosclerotic disease, in whom acute release of inflammatory mediators can induce either coronary artery spasm alone, or plaque erosion or rupture manifesting as acute myocardial infarction with its consequences. A type III variant of Kounis syndrome has been described recently in patients with coronary artery stent thrombosis in whom aspirated thrombus specimens stained with hematoxylin–eosin and Giemsa are found infiltrated by eosinophils and mast cells, respectively.

The second patient had positive skin prick tests in latex and atracarium but the other drugs he received during anesthesia such as propofol, fentanyl and sevoflurane could also contribute to the allergic cascade. Therefore, this patient was under the risk of five agents which were able to act directly or via IgE mechanism to degranulate mast cells. It is known that mast cell surface bears 500,000 to 1 million IgE molecules and degranulation occurs when 2,000 of these molecules, which is a critical number, make 1,000 bridges with antigens. These bridges can be made with antigens of different specificities as it happens in patients during anesthesia [2]. It looks likely that the more antigens an anesthetized patient is exposed to, the easier and quicker the degranulation occurs.

It is generally believed, that myocardial involvement during severe anaphylactic reactions is the result of systemic vasodilatation, reduced venous return, leakage of plasma and volume loss due to increased vascular permeability that ensue leading to depression of the cardiac output, and contribute to coronary hypoperfusion with subsequent myocardial damage.

However, experimental and clinical studies have shown that human heart is the primary site and the target of

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anaphylaxis resulting in the development of Kounis syndrome.

It has been shown [3] that, in experimental anaphylaxis, cardiac output decreases by 90 %, left ventricular end diastolic pressure increases significantly by 35 % indicating pump failure, arterial blood pressure increases significantly by 35 %, and starts declining steadily after 4 min. Concurrently, electrocardiographic changes show signs of acute myocardial ischemia. All these show that anaphylactic cardiac disease is not due to peripheral vasodilatation. 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 other experiments [4], the anaphylactic cardiac damage is dissociated temporarily into an initial primary cardiac reaction caused by intracardiac release of histamine, and a subsequent cardiovascular reaction secondary to systemic release of mediators. Studies with isolated guinea pig hearts [2] undergoing anaphylaxis following intra-aortic injection of antigen, show an abrupt heart rate increase reaching a peak within 2 min, a transient increase in ventricular contractile force followed by a prolonged decrease, and a prompt and prolonged decrease in coronary blood flow.

In an Italian clinical study [5] concerning five patients with spontaneous angina, four of whom had significant (greater than 70 % stenosis) coronary artery disease and one with normal coronaries after infusion of histamine, with pre-treatment with cimetidine to antagonize H₂ receptors, two of the five patients (40 %) developed angina during histamine infusion, accompanied by ST-T elevation,

decreased coronary blood flow, increased coronary vascular resistance, but with no significant changes in the mean arterial blood pressure. During the histamine-induced angina, one patient developed coronary arterial spasm indicating that stimulation of the H₁ receptor induces a reduction of coronary blood flow either from vasodilatation of small coronary resistance vessels, or from stimulation of vasoconstricting H₁ receptors of large epicardial coronary arteries.

All the above clinical and experimental studies indicate that during anaphylaxis the heart and the coronary arteries, in particular, constitute the early and primary target resulting in Kounis syndrome. This is being confirmed in a clinical study, we have in progress, according to which high sensitivity specific cardiac troponins are raised in cases of severe anaphylactic reactions.

Conflict of interest None.

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