Anaphylactic Shock: Kounis Hypersensitivity-Associated Syndrome Seems to be the Primary Cause

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Abstract

Experiments have shown that anaphylaxis decreases cardiac output; increases left ventricular end diastolic pressure; induces severe early acute increase in respiratory resistance with pulmonary interstitial edema; and decreases splanchnic, cerebral, and myocardial blood flow more than what would be expected from severe arterial dilation and hypotension. This is attributed to the constrictive action of inflammatory mediators released during anaphylactic shock. Inflammatory mediators such as histamine, neutral proteases, arachidonic acid products, platelet-activating factor (PAF), and a variety of cytokines and chemokines constitute the pathophysiologic basis of Kounis hypersensitivity-associated acute coronary syndrome. Although the mechanisms of anaphylactic shock still remain to be elucidated, myocardial involvement due to vasospasm-induced coronary blood flow reduction manifesting as Kounis syndrome should be always considered. Searching current experimental and clinical literature on anaphylactic shock pathophysiology, causality, clinical appearance, and treatment via PubMed showed that differentiating global hypoperfusion from primary tissue suppression due to mast cell mediator constrictive action on systemic arterial vasculature is a challenging procedure. Combined tissue suppression from arterial involvement and peripheral vasodilatation, perhaps, occur simultaneously. In cases of anaphylactic shock treatment targeting the primary cause of anaphylaxis together with protection of coronary vasculature and subsequently the cardiac tissue seems to be of paramount importance.

Keywords: Anaphylaxis, Anaphylactic shock, Kounis syndrome, Respiratory resistance, Respiratory reactance, Vascular resistance

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Introduction

It is generally believed, that during anaphylactic shock, the observed myocardial damage and ventricular dysfunction is the result of depression of cardiac output due to coronary hypoperfusion from systemic vasodilation, leakage of plasma and volume loss due to increased vascular permeability, and reduced venous return. It has been reported that during anaphylactic shock circulating blood volume may decrease by as much as 35% within 10 min due to transfer of intravascular fluid to extravascular space.[1] Furthermore, severe vasodilation resistant to epinephrine and responding only to other potent vasoconstrictors has been also reported.[2]

This effective shift of fluid volume is countered by compensatory vasopressor mechanisms involving the release of epinephrine and norepinephrine together with activation of angiotensin system.[3] The ensuing increase in catecholamines might produce varied effects. Some patients during anaphylactic episodes experience maximum peripheral vasoconstriction due to increased vascular resistance while others have decreased systemic vascular resistance. The variable effects of internal compensatory mechanisms might explain why epinephrine injections sometimes fail to help acute and severe allergy. 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 even in the absence of existing coronary disease.[4,5] Indeed, platelets from patients suffering from angina pectoris are more sensitive to increased endogenous serum epinephrine levels and

therefore are prone to get activated and aggregate in order to induce thrombotic events.[6] In anaphylactic shock, experiments with ovalbumin-sensitized guinea pigs[7] have shown that left ventricular end diastolic pressure raises within 3 min following antigen challenge; while, contemporarily, cardiac output declines by 90%. These have forced the researchers to conclude that the view of registered anaphylactic cardiac damage might be due to peripheral vasodilatation should be definitively excluded. Other recent experimental findings[8] have shown that during anaphylactic shock the cerebral blood flow decreases more than what would be expected from severe arterial hypotension. This was attributed to the early and direct action of anaphylactic mediators on cerebral vessels. Concurrent changes in airway-lung mechanics, such as respiratory resistance and reactance response to ovalbumin-induced anaphylactic shock in allergic rats have been also studied.[9] It was found that an early increase in respiratory resistance followed by a decrease in respiratory reactance consistent with initial acute bronchoconstriction occurs and this is followed by pulmonary capillary leakage into smaller airspaces.

The above experimental findings in heart, brain, and lungs show that coronary vasoconstriction cerebral vasospasm and bronchoconstriction are the initial events during anaphylactic shock. These findings together with clinical observations according to which anaphylactic myocardial damage responds to myocardial infarction protocol treatment and not only to fluid replacement, might have profound implications in pathophysiology of anaphylactic shock and also clinical and therapeutic implications as far as Kounis hypersensitivivity-associated syndrome is concerned.[10-13]

Kounis Syndrome: The Hypersensitivity Coronary Disorder

The association of allergic, anaphylactic, and anaphylactoid reactions with acute coronary events had been observed more than 6 decades ago and cases of allergic myocardial infarction were published in 1965.[14] However, a detailed description of the allergic angina syndrome, which could progress to acute allergic myocardial infarction, was not described until 1991.[15] Following this initial description, other researchers emphasizing the existence and association of this syndrome with coronary inflammation and vasospastic angina gave recognition, name, attention, and emergence to this life-threatening clinical phenomenon.[16,17] Today allergic angina and allergic myocardial infarction,[18] that are referred to as 'Kounis syndrome', are ubiquitous diseases affecting from pediatric to geriatric patients, involving numerous and continuously increasing causes, with broadening clinical manifestations and covering a wide spectrum of mast cell activation disorders. It has been repeatedly stated that Kounis syndrome is not a rare disease but a rarely diagnosed condition.[19] Kounis syndrome is regarded as nature's own experiment and magnificent natural paradigm which might have profound clinical and therapeutic implications and may shed light on potential therapeutic strategies that may apply to the area of interference with plaque erosion or rupture and primary as well as secondary prevention of acute coronary and cerebrovascular events.[20] The number of causes that have been implicated to induce Kounis syndrome is increasing rapidly. These include various drugs, environmental exposures, and several conditions.[21] The most recent offender was Anisakis simplex.[22] Other recent offenders include scombroid syndrome,[23] which is also called histamine fish poisoning; gelofusin substance;[24] latex exposure;[25] losartan;[26] systemic mastocytosis; and mast cell activation syndromes.[27] Anisakis simplex is a common fish parasite which can sensitize humans and induce anisakiasis and Kounis syndrome. On the other hand, fish flesh contains the aminoacid histidine and when fish is infected by gram negative bacteria which contain the enzyme histidine decarboxylase, this enzyme converts histidine to histamine which induces Kounis syndrome. The gelofusin substance is a bovine gelatin administered to maintain intravascular volume. Gelofusin is component of various vaccines for children and constitutes the main cause of sensitization to children. It should be always remembered the "kiss of death"[21] and the "dog licking".[21] "The kiss of death" occurs when a person after consumption of shellfish or peanuts kisses or exhales allergens during oral contact with a person who happens to be allergic to these substances. Furthermore a dog, who receives antibiotic such as penicillin for any infection, can be very dangerous when he or she, in a gesture of compliance licks his penicillin allergic master or other associates. Kounis syndrome is manifesting with three variants: Coronary artery spasm, myocardial infarction, and stent thrombosis.[28] The currently used bare metal coronary stents are made from metal platform which is stainless steel containing nickel, chromium, titanium, manganese, and molybdenum. In the drug eluting coronary stents the metal platform is covered by the polymer coating with impregnated antiproliferative drugs. All these components constitute an antigenic complex that applies continuous, persistent, repetitive, and chronic inflammatory irritation on the arterial intima lasting as long as the antigens stay present. That is why some unexpected, peculiar, bizarre, strange, surprising, extraordinary, and astonishing reports are appearing in the medical literature. According to these reports, patients with implanted stents who accidentally developed an allergic reaction elsewhere in the human body from various causes are prone to develop, contemporarily intrastent thrombosis culminating in deadly anaphylactic cardiac shock. Indeed, such stent thrombosis has been

associated with allergic symptoms such as glottis edema, cold sweat, and tongue enlargement followed flavonate-propyphenasone administration a week after stent implantation,[29] intravenous administration of the non-anionic contrast material iopromide during routine excretory urography,[30] nonsteroidal anti-inflammatory agent acemetacine manifesting as type III variant,[31] and anaphylaxis after insect and larvae stings.[32] Even the astonishing event that allergy to clopidogrel, the drug given to prevent stent thrombosis, has induced itself stent thrombosis.[33] The incidence of anaphylaxis with cardiovascular features is about eight per 100,000 population in both Europe and USA.[34,35] Cardiovascular symptoms are more common in events occurring in the operating room and are associated mainly with muscle relaxants and latex.[36] In a cohort including children from 3 to 14 years, the incidence of anaphylaxis with cardiovascular symptoms including hypotension, tachycardia, and cardiac arrest was 20.5%.[37] In a study on 29 fatalities from Hymenoptera stings, the performed autopsy in 12 fatalities revealed 11 with cardiac disease, 10 of which had coronary heart disease.[38] So far, there are 20 published cases of anaphylactic shock associated with Kounis syndrome. These cases include patients who did not respond to antianaphylactic treatment, but required additional myocardial infarction protocol therapy. This clinical evidence, together with experimental findings, supports the view that anaphylactic shock is the result of depression of cardiac output due to coronary hypoperfusion from vasoconstrictive action of anaphylactic mediators on the coronary tree and not only from systemic vasodilation. Type I and type II variants of Kounis syndrome[21] include such patients with normal or nearly normal coronary arteries and patients with culprit, but quiescent preexisting atheromatous disease in whom the acute release of anaphylactic mediators can induce either coronary artery spasm or coronary artery spasm together with plaque erosion or rupture culminating in acute myocardial infarction with anaphylactic cardiac shock.

Experimental Evidence

In a recent experiment in rats,[39] it was shown that vascular resistance responses to anaphylactic shock were characterized by considerable increase in portal venous resistance, initial transient decrease in hepatic artery and splanchnic vascular resistances, and absence of a significant increase in splanchnic vascular resistances in the early stage. This opposes to the general belief that anaphylactic shock is the result of diminished vascular resistance leading to vasodilation and fluid extravasation. The increased portal venous resistance is attributed to anaphylaxis-released vasoactive mediators which constrict portal veins in isolated perfused rat livers.[40]

In another experiment,[41] left ventricular pressure, coronary artery, and coronary vein pressures and coronary flow were directly and simultaneously measured before and after ovalbumin challenge in both antigen-sensitized and in nonsensitized rat hearts with induced coronary flow reduction. The authors determined maximum increasing rate of left ventricular pressure (dp/dtmax) during isovolumic contractions for the assessment of left ventricular contractility without changes in preload. They applied also the cross-circulated blood perfusion method, which permits analysis of left ventricular mechanical work in the excised heart under more physiological conditions. They concluded that coronary vasoconstriction inducing myocardial ischemia, during anaphylaxis, is the main and major contributory factor for the ensuing ventricular dysfunction. Furthermore, in the studies with ovalbumin-sensitized guinea pigs,[7] it was shown that soon after antigen administration, electrocardiogram showed signs of acute myocardial ischemia, cardiac output was decreased by 90%, left ventricular end diastolic pressure was raised indicating pump failure, and arterial blood pressure was increased. Blood pressure started declining steadily after 4 min. It was concluded that the rapid increase in left ventricular end diastolic pressure suggests that volume loss due to an increase in vascular permeability and decreased venous return were unlikely to have been the primary causes of the documented depression in cardiac output. It was concluded that the view of registered anaphylactic cardiac damage might be due to peripheral vasodilatation should be definitively excluded.[7] In another experiment,[42] passively sensitized guinea pigs with anti-albumin rabbit serum and challenged with albumin, showed heart rate and left ventricular end diastolic pressure markedly increased; while coronary flow, aortic flow, left ventricular developed pressure, and dp/dtmax profoundly decreased. When specific platelet-activating factor (PAF) antagonist was administered, the increased heart rate and left ventricular end diastolic pressure as well as the decrease in coronary and aortic flow, left ventricular developed pressure and dp/dtmax were all inhibited in a dose dependent manner. PAF is mast cell mediator deriving from mast cell degranulation in anaphylaxis and its neutralization by its antagonist results in inhibition of primary events of anaphylaxis on coronary blood flow and other parameters. In isolated guinea pig, hearts undergoing anaphylaxis after an intra-aortic injection of antigen,[43] a prompt and prolonged decrease in coronary blood flow, an abrupt heart rate increase that peaked within 2 min, and a transient increase in ventricular contractile force followed by a prolonged decrease were observed. These findings are in accordance with those from other reports that anaphylactic cardiac damage may be dissociated temporarily into two sets

of events: Initial primary cardiac reaction caused by the intracardiac release of histamine and a subsequent cardiovascular reaction secondary to the systemic release of mediators.[44]

In the study of Davidson,[8] it was found that anaphylactic shock decreases cerebral blood flow more than what would be expected from severe arterial hypotension. The authors of this paper concluded that, in anaphylactic shock, severe impairment of the cerebral blood flow takes place which could not be explained by the level of arterial hypotension. In these experiments, with use of rat model of anaphylaxis, the tissue oxygen partial pressure decreased very rapidly, as early as 1 min following the onset of anaphylaxis and this was attributed to the early and direct action of anaphylactic mediators on cerebral vessels. Indeed, mast cell mediators such as histamine, chymase, and leukotrienes can induce cerebral artery spasm and PAF can reduce cerebral blood flow leading to postischemic hypoperfusion. Therefore, cerebral ischemia and brain injury following anaphylactic shock could be due to direct action of anaphylactic mediators on the cerebral arterial system and not solely due to arterial hypotension. Another experimental study[45] has shown that antigen challenge in the small isolated mesenteric and coronary arteries from the sensitized guinea pig is followed by anaphylactic contraction but not relaxation. The released NO from the endothelium of small arteries, during the antigen challenge, contributes to the development of hypotension or redistribution of blood during anaphylaxis. However, the contracting products of cyclooxygenase pathway are very important for the development of the small artery constriction in anaphylactic shock and counteract the development of the relaxation and hypotension. The authors of this study concluded that arterial contraction induced by anaphylaxis could be partially attenuated by the endothelium-derived NO and enhanced by the cyclooxygenase products in the small coronary and mesenteric arteries. All the above experimental evidence supports the view that the primary target of the released anaphylactic mediators is the arterial vasculature resulting in damage of the corresponding myocardial or brain tissue and the bronchial tree responding with severe early and acute bronchoconstriction.

Clinical Evidence

There are, currently, patients with anaphylactic cardiac shock who do not respond to intravenous fluid administration and antiallergic therapy, but required coronary event treatment protocol. The following reports have been published this year. In a patient with Hymenoptera sting-induced Kounis syndrome complicated with anaphylactic shock,[46] urgent coronary angiography revealed acute coronary thrombosis and the patient recovered with intra-aortic balloon pump assistance

and myocardial infarction treatment. In another patient,[47] who was stung by multiple wasps and developed type I variant of Kounis syndrome with anaphylactic shock and myocardial ischemia, treatment with 2 l of normal saline, adrenaline, hydrocortisone, and antihistamines did not have any immediate effect and the patient recovered in a later stage with vasopressors and myocardial infarction protocol treatment. In an atopic female nurse[48] with previous atopic eczema, asthma, and allergy to milk protein; who suffered an anaphylactic reaction, hemodynamic status was unresponsive to intravenous administration of fluids such as Ringer's acetate and antiallergic treatment with adrenaline and corticosteroids. Her condition was complicated with pulmonary congestion with reduced ejection fraction. The patient recovered with myocardial infarction protocol treatment. It was commented that hemodynamic disturbance was most probably due to myocardial stunning leading to reduced cardiac output rather than due to fluid extravasation. In a patient with per-operative anaphylactic shock due to gelofusin infusion[24] treatment with metaraminol and epinephrine worsened the hypotension and the cardiac output was lost. The patient recovered gradually with intravenous antihistamines, steroids, and inotropic support. Finally, in a patient with stent thrombosis following snake bite,[49] which today is regarded as anaphylactic consequence, the patient was not responding to inotropes and fluid expansion but he recovered with thrombolysis and other acute myocardial infarction protocol treatment.

Conclusion

Although the mechanisms of anaphylactic shock still remain to be elucidated, bronchial and myocardial involvement with early severe bronchoconstriction and vasospasm-induced coronary blood flow reduction manifesting as Kounis syndrome respectively should be always considered. Combined bronchoconstriction with interstitial edema and tissue suppression from arterial involvement and peripheral vasodilatation, perhaps, occur simultaneously. Therefore, in any case of anaphylactic shock combined treatment targeting the primary cause of anaphylaxis together with protection of lung and cardiac tissue seems to be of paramount importance. More studies and more experience are needed to determine the importance of mediators of anaphylaxis in myocardial pathobiology.

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