

Combined etiology of anaphylactic cardiogenic shock: Amiodarone, epinephrine, cardioverter defibrillator, left ventricular assist devices and the Kounis syndrome

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ABSTRACT

Anaphylactic shock is a life-threatening condition which needs detailed and meticulous clinical assessment and thoughtful treatment. Several causes can join forces in order to degranulate mast cells. Amiodarone which is an iodine-containing highly lipophilic benzofuran can induce allergic reactions and anaphylactic shock in sensitized patients. Epinephrine is a life saving drug, but in sulfite allergic patients it should be given with caution due its metabisulfite preservative. Metals covering cardiac defibrillators and pacemakers can act as antigens attached to serum proteins and induce allergic reactions. In anaphylactic shock, myocardial involvement due to vasospasm-induced coronary blood flow reduction manifesting as Kounis syndrome should be always considered. 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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INTRODUCTION

Acute myocardial infarction, vasospastic angina and even stent thrombosis can manifest as Kounis hypersensitivity-associated coronary syndrome when follow an allergic, hypersensitivity, anaphylactic or anaphylactoid episode.^[1] This syndrome is the result of the action of inflammatory mediators released locally or in the systemic circulation following mast cell degranulation. The released mediators can induce either coronary artery spasm which can progress to acute myocardial infarction or atheromatous plaque erosion or rupture culminating to coronary thrombosis. Vasospastic angina (type I), acute coronary thrombosis (type II) and stent thrombosis (type III) are the three variants of this syndrome that have been described so far. The allergic thrombotic process can also

follow activation, by mast cell mediators, of high affinity and low affinity FC γ RI, FC γ RII, FC ϵ RI and FC ϵ RII receptors situated in the platelet surface.^[2] It has been found that mast cells degranulate when 2000 nearby antibodies attached to their surface are bridged by corresponding antigens and make the critical number of 1000 bridges. This can be achieved by antibodies of different specificities and especially in children the combination of several exposures at a given time is related to disease severity.^[3] Today, Kounis syndrome is ubiquitous disease affecting patients of any age, from 2 years old to octagenarians, involving numerous and continuously increasing causes, with broadening clinical manifestations.^[4,5] Multiple combined etiologies can join forces and induce anaphylaxis and Kounis syndrome. Amiodarone is used as anti-arrhythmic agent and in combination with arrhythmogenic drugs

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can induce anaphylaxis as it has been reported recently in the *Annals of Cardiac Anesthesia*.^[6,7] In addition, anaphylactic cardiogenic shock following amiodarone administration has occurred in a 15-year-old boy with a history of tuberous sclerosis, and a large nonobstructive cardiac rhabdomyoma in the left ventricle.^[8] The patient had tumour-associated ventricular tachycardia episodes. Despite treatment with inotropes and epinephrine his condition worsened with severely depressed biventricular function necessitating support with left ventricular assist device, the centrifugal Rotaflow (Maquet, Gentige group, Rastatt, Germany). His electrocardiogram showed myocardial ischemia with ST segment elevation in the inferior and lateral leads. He received methylprednisone for a 5-day course for anaphylactic shock had a good recovery and was discharged home with normal systolic function and baseline neurologic status. The patient had cardioverter defibrillator implantation due to episodes of unstable ventricular tachycardia and had been subjected to several amiodarone exposures in the past. The authors of this report wondered whether this was a case of Kounis syndrome or was the result of epinephrine administration. These reports, really, raise important questions especially when amiodarone, epinephrine, cardioverter defibrillator, left ventricular assist devices, anaphylactic cardiogenic shock are combined in anesthetized cardiac patients.

AMIODARONE-INDUCED ALLERGIC REACTIONS

Most of the severe systemic adverse reactions of amiodarone are well known and concern skin, lung, thyroid gland, liver peripheral nerves and platelets. This drug is an iodine-containing highly lipophilic benzofuran derivative serving a class III long-acting anti-arrhythmic, capable of blocking both α and β -adrenoceptors. The incidence of amiodarone-induced hypersensitivity reactions in hospitalized patients with a listed allergy to iodine or iodinated contrast agents was found to be <1%.^[9] Severe anaphylactic reactions with cardiogenic shock are rare and only 2 additional cases have been reported^[6,10] since the publication of Averin *et al.*^[8] However, iodinated contrast media have induced Kounis syndrome on several occasions.^[11,12] In a recent study^[13] concerning patients with amiodarone-induced thrombocytopenia it was found that this was caused by drug-dependent antibodies specific for platelet glycoproteins GPIa/IIa and/or GPIIb/IIIa. The authors of this study postulated that *in vivo*, amiodarone may become incorporated into occult lipophilic domains in platelet glycoproteins, producing structural modifications that

are immunogenic in some individuals, and that the resulting antibodies can cause platelet destruction in individuals taking this drug.

EPINEPHRINE ADMINISTRATION IN ANAPHYLAXIS

Exogenous epinephrine administration is a life saving procedure, but it has been shown to promote platelet activation via specific receptors found on the platelet surface, it also induces platelet aggregation by increasing platelet production of thromboxane B₂ and heightening platelet sensitivity to adenosine diphosphate and promotes thrombin induced binding of platelets to fibrinogen.^[14] Epinephrine can aggravate, therefore, myocardial ischemia, prolong QTc interval, and induce coronary vasospasm and arrhythmias. Elderly patients, especially with a history of hypertension and coronary artery disease, are prone to these side effects. In patients who may have received β -blockers in the initial management of the acute coronary syndrome, the usual dose of epinephrine may be ineffective. It may also promote more vasospasm due to unopposed alpha adrenergic effect. Furthermore, commercially available preparations of epinephrine usually contain as a preservative, sodium metabisulfite. This substance is commonly used as an antioxidant in the food and pharmaceutical preparations. There are reports of hypersensitivity, anaphylaxis, and even death from Kounis syndrome from sulfite administration. Anaphylactoid shock has been reported during epidural anesthesia for cesarean section, in which the responsible agent was metabisulfite, as additive agent of epinephrine-containing local anesthetic.^[15] This situation poses a therapeutic dilemma in the sulfite-sensitized patients who suffer from anaphylactic shock. Physicians dealing with anaphylactic shock should be aware of this treacherous association. Although epinephrine is still the primary drug for anaphylaxis, avoidance of medications that contain metabisulfites as preservatives, including epinephrine, is suggested for patients with definite sensitization to sulfites. In this situation, a possible alternative is glucagon which has been used successfully for treatment of anaphylaxis in patients taking β -blockers.^[16] Fortunately, for patients sensitive to sulfites, sulfite-free epinephrine is already commercially available (American Regent Inc., USA).

CARDIOVERTER DEFIBRILLATORS AND LEFT VENTRICULAR ASSIST DEVICES POTENTIAL ALLERGENIC DEVICES

Cardioverter defibrillators as well as cardiac pacemakers have generators which are covered with titanium,

conductor wires consisting of an alloy of nickel, cobalt, chromium and molybdenum and pacing electrodes which are made of platinum alloyed with 10–20% iridium.^[17] Metal anions eluted from nickel, cobalt, chromium molybdenum and titanium can attach to circulating proteins and act as haptens that behave as allergic sensitizers. Allergy to nickel can occur in up to 24.6% of the population and is the most frequent cause of allergic contact dermatitis.^[18] It is also common that patients are sensitized to multiple metal anions. Concurrent sensitization, cross-reactivity or both seem to be possible. It has been shown that sensitization to one metal anion increases the possibility of being sensitized to additional metals. Metals can also “join forces” in order to sensitize individuals. Recently, an increased rate of thrombosis with substantial morbidity and mortality has been reported with the use of HearMate II (Thoratec, Pleasanton, CA, USA) left ventricular assist device.^[19] Histology of thrombotic material, deposited near inflow bearing, showed the presence of lymphocytes, plasma cells and eosinophils thus denoting hypersensitivity reaction. Titanium alloy can induce hypersensitivity and immune dysfunctions rendering titanium no longer biologically inert.^[20] In the patient reported by Averin *et al.*^[8] a temporary left ventricular assist device, the centrifugal Rotaflow (Marquet), was used which is the only centrifugal pump that comes without a seal or a metal shaft. However, this patient had cardioverter defibrillator implanted with titanium coverage and metallic conductor wires and pacing electrodes able to induce allergic reaction.

ISCHEMIC MYOCARDIAL DAMAGE AS PRIMARY EVENT IN ANAPHYLACTIC SHOCK

Experimental studies have shown that during anaphylaxis acute myocardial ischemia, decrease in cardiac output, initial rise in arterial blood pressure and increase in left ventricular end diastolic pressure indicating pump failure are the main findings. The latter, according to the authors, definitely excludes peripheral vasodilatation as a cause of the registered anaphylactic cardiac damage.^[21] Clinically there are patients with anaphylactic shock and Kounis syndrome who do not respond to fluids, hydrocortisone, antihistamines and vasopressors but need myocardial infarction protocol treatment.^[22] Indeed, in one patient treatment with metaraminol and epinephrine worsened hypotension and annihilated cardiac output.^[23] Therefore, myocardial dysfunction due to vasospasm-induced coronary blood flow reduction manifesting as Kounis syndrome should be always considered in cases of anaphylactic shock.

INCIDENCE OF KOUNIS SYNDROME

The incidence of anaphylaxis with circulatory symptoms during a 3-year period was estimated in a retrospective study.^[24] In this study, 226 individuals suffered 246 episodes of severe life-threatening anaphylaxis with cardiovascular symptoms, with an incidence of 7.9–9.6 per 100,000 inhabitants per year. The case–fatality rate was 0.0001%.^[24] As far as Kounis syndrome is concerned, owing to missed and/or undiagnosed cases and a lack of large prospective trials, determining the prevalence and exact incidence is difficult with our current state of knowledge. Although it is considered to be not a rare disease, it is infrequently reported in the literature and recognized in clinical practice.^[25] Recent reports have shown that Kounis syndrome has been observed in every race, age group (from 2 to 90 year olds) and geographic location. Increased awareness about its existence and conduction of large prospective trials will help in true estimation of its incidence.^[26] In the district of Achaia, Greece with a population of 300,000 inhabitants, and with increased awareness for the existence of Kounis syndrome, 52 cases of this syndrome have been encountered in the last 4 years caused by environmental exposures, drug allergies and stent implantation. The annual incidence of Kounis syndrome in this district was estimated of 4.33 cases/100,000 inhabitants.^[1] In a tertiary hospital in Istanbul, Turkey, a total of 3876 patients underwent urgent coronary angiography for suspected acute myocardial infarction during a 3-year period (2006–2009) and eight patients were diagnosed with Kounis syndrome. Thus, the catheterization laboratory prevalence of Kounis syndrome is estimated to be 0.002%^[25] Kounis syndrome has mostly been reported in southeastern Europe, especially Greece, Spain, Italy and Turkey. This geographical variation could be attributed to the increased awareness of physicians of the existence of Kounis syndrome, climate and environmental conditions, resulting in pollen cross-reactivities and hymenoptera exposures, overconsumption of medicines, or inadequacy of preventative measures. Gene–environment interactions starting in early life using the epigenetic approach should be also explored too.^[1]

CONCLUSION

Multiple combined causes including drugs and devices can join forces able to induce anaphylactic shock. Patients simultaneously exposed to various corresponding allergens that can bridge antibodies

with different specificities, are at increased risk. These patients have more symptoms than mono-sensitized individuals. The heart and the coronary arteries, in particular, seem to be primary sites of anaphylaxis. Combined treatment targeting the primary cause of anaphylaxis together with protection of cardiac tissue seems to be of paramount importance.

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