

Kounis syndrome: a new twist on an old disease

Nicholas G Kounis¹, Andreas Mazarakis¹, Grigorios Tsigkas², Sotiris Giannopoulos³ & John Goudevenos⁴

¹Department of Cardiology, 'Agios Andreas' State General Hospital, Patras, Greece

²Department of Cardiology, University of Patras Medical School, Patras, Greece

³Department of Neurology, University of Ioannina, School of Medicine, Ioannina, Greece

⁴Department of Cardiology, University of Ioannina, School of Medicine, Ioannina, Greece

[†]Author for correspondence: Department of Medical Sciences, Patras Highest Institute of Education & Technology, Queen Olga's Square, 7 Aratou Street, Patras 26221, Greece ■ Tel.: +30 2610 279579

■ Fax: +30 2610 279579 ■ ngkounis@otenet.gr

Kounis syndrome is the concurrence of acute coronary syndromes with conditions associated with mast cell activation, such as allergies or hypersensitivity and anaphylactic or anaphylactoid insults that can involve other interrelated and interacting inflammatory cells behaving as a 'ball of thread'. It is caused by inflammatory mediators such as neutral proteases including tryptase and chymase, arachidonic acid products, histamine, platelet activating factor and a variety of cytokines and chemokines released during the activation process. Platelets with FCεRI and FCεRII receptors also participate in the above cascade. Vasospastic allergic angina, allergic myocardial infarction and stent thrombosis with occluding thrombus infiltrated by eosinophils and/or mast cells constitute the three reported variants of this syndrome. Kounis syndrome is a ubiquitous disease that represents a magnificent natural paradigm and nature's own experiment, in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture. Kounis syndrome can complicate anesthesia, vaccination, medical therapy and stent implantation and it seems to be associated with coronary allograft vasculopathy and takotsubo syndrome, it can often be confused with hypersensitivity myocarditis and can be the cause of unexplained sudden death. Kounis syndrome has revealed that the same mediators released from the same inflammatory cells are present in acute coronary events of nonallergic etiology. These cells are not only present in the culprit region before plaque erosion or rupture but they release their contents just before an actual coronary event. Therefore, does Kounis syndrome represent a magnificent natural paradigm and nature's own experiment in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture showing a novel way towards our effort to prevent acute coronary syndromes? Drugs, substances targeting the stem cell factor that is essential for mast cell development, proliferation, survival, adhesion and homing as well as monoclonal antibodies and natural molecules that protect mast cell surface and stabilize mast cell membrane could emerge as novel therapeutic ways capable to prevent acute coronary and acute cerebrovascular events.

Three words, taken from the Hellenic vocabulary, constitute the main cornerstones of today's immunology:

- 'Anaphylaxis' (from Hellenic *aphylaxis* = *no phylaxis*, meaning without protection, whereas prophylaxis means protection) was introduced by the French physiologists Paul Portier and Michael Richet in 1902, when they described a dog that developed cardiorespiratory arrest and died after injection of a jellyfish toxin called actinotoxin, although 14 days earlier the dog had well tolerated the same injection [1]. Both scientists were awarded the Nobel Prize in Medicine and Physiology in 1913;
- 'Allergy' (from Hellenic *allergia* = *allo ergo*, meaning altered capacity to react) was coined

in 1906 by the Viennese pediatrician and immunologist Clements von Piquet, who recognized that in both protective immunity and hypersensitivity reactions, antigens had induced changes in reactivity [2];

- 'Atopy' (from the Hellenic *atopos* = *no topos*, meaning out of place) which is often used to describe IgE-mediated diseases (Box 1).

An important contributor in allergy, atopy and anaphylaxis is a unique cell named by Paul Erlich in 1887 as a 'mast cell' because of its numerous metachromatic granules, which reminded him of a 'well-fed cell' (*mastzellen* in German) [3]. Mast cells are ubiquitous in the human body, including the brain, which does not suffer from allergic reactions because IgE antibody complexes do not

Keywords

- allergic angina ■ allergic myocardial infarction
- anesthetic drugs
- coronary allograft vasculopathy ■ eosinophilic coronary arteritis ■ heart, brain and Kounis syndrome
- hypersensitivity myocarditis
- Kounis syndrome
- stent thrombosis
- Takotsubo syndrome

Box 1. Medical terms associated with Kounis syndrome.

- Hypersensitivity: an excessive reaction associated with gross tissue changes after antigen–antibody (IgE or IgM) reaction
- Allergy: synonymous to hypersensitivity and means an altered capacity to react
- Anaphylaxis (whereas prophylaxis in Greek means ‘protection’, (an)aphylaxis means ‘opposite protection’ or ‘against protection’): a state of life threatening severe hypersensitivity induced by exposure to certain kind of antigens
- Anaphylactoid reaction: a reaction with similar clinical picture as allergic, hypersensitivity, or anaphylactic that is not IgE-mediated
- Atopy: a genetic predisposition to produce significant amounts of antibodies
- Arthus type reaction (Arthus, 1903): local anaphylaxis with edematous, erythematous or hemorrhagic reaction
- Idiosyncrasy: an inherent qualitatively abnormal reaction to a drug due to genetic predisposition
- Intolerance: a low threshold to the normal pharmacological action of a drug

cross the blood–brain barrier. Mast cells preform and store approximately 500 secretory granules and many others which are made *de novo* and are released locally and in systemic circulation when specific antigens react with IgE antibodies attached to mast cells and induce mast cell degranulation. This degranulation resembles a bag of popcorn ‘popping’ until the contents overflow [4] and occurs only in approximately 10% of atopic individuals. Mast cells have been linked to many human organs and systems and, as has been stated by Theoharides, their role is versatile and compels a more appropriate name to indicate its polydimensional potential [5], perhaps ‘pleiotropocyte’ (multifaceted cell in Hellenic).

Despite cardiovascular symptoms and signs being the main clinical manifestations associated with allergic or hypersensitivity and anaphylactic or anaphylactoid attacks, it was not until six decades ago, when Pfister reported a 49-year-old man who developed anteroseptal myocardial infarction and urticaria after 4 days of treatment with 300,000 units/day penicillin in oil. The patient was treated with dicumarol, papaverine, morphine and diphenhydramine hydrochloride [6].

In 1991, Kounis and Zavras described the syndrome of allergic angina as the concurrence of chest pain and allergic reactions, accompanied by clinical and laboratory findings of classical angina pectoris caused by inflammatory mediators released during the allergic insult [7]. Allergic angina could progress to acute myocardial infarction which was named allergic myocardial infarction [8–10].

In 1995, Kovanen *et al.* examined specimens of coronary arteries from 20 patients who had died of acute myocardial infarction and found that the degree of mast cell degranulation was much higher (200:1) at the sites of plaque erosion or rupture than

in adjacent areas or in the more distant unaffected areas [11]. He concluded that collagen-degrading proteases, from mast cells, could induce plaque erosion and/or rupture. Following this clinical description, in 1995 Constantinides raised the possibility that “even ordinary allergic reactions could promote plaque disruption” [12]. This was based on Constantinides’s observation that circulating mast cell precursors could penetrate the open junctions between endothelial cells that line human atheromatous plaques in contrast to closed junctions over the normal arterial intima [13]. In 1998, Braunwald categorized allergic angina in a subgroup of dynamic coronary occlusion lesions by stating that “allergic reactions with mediators such as histamine or leukotrienes acting on coronary vascular smooth muscle” can induce vasospastic angina [14].

Today, allergic angina and allergic myocardial infarction is a ubiquitous disease covering a wide spectrum of mast cell activation disorders that are referred to as ‘Kounis syndrome’ [15–17] and are described in major cardiovascular textbooks [18], as a new clinical entity.

Kounis syndrome is regarded as a magnificent natural paradigm and nature’s own experiment 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.

Definition & pathophysiology of Kounis syndrome

Kounis syndrome is defined as the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells, and including allergic or hypersensitivity and anaphylactic or anaphylactoid attacks. 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 [15–17]. A subset of platelets bearing FCεRI and FCεRII receptors are also involved in the activation cascade [19]. All of these inflammatory cells participate in a vicious inflammatory cycle and via multidirectional signals:

- Mast cells can enhance T cell activation [20];
- T cells can mediate mast cell activation and proliferation [21];

- Inducible macrophage protein-1 α can activate mast cells [22];
- Mast cells can activate macrophages [23];
- T cells can regulate macrophage activity [24].

During hypersensitivity or during an allergic blow up, degranulation of mast cells is taking place and a variety of stored and newly formed inflammatory mediators are released locally and within the systemic circulation [25], which include: biogenic amines such as histamine, chemokines, enzymes such as neutral proteases, chymase, tryptase, cathepsin-D, peptides, proteoglycans, cytokines, growth factors and arachidonic acid products such as leukotrienes, thromboxane, prostacyclin and platelet activating factor (PAF). Some of these mediators such as histamine, neutral proteases including tryptase, chymase and cathepsin-D, as well as arachidonic acid products such as leukotrienes, PAF and thromboxane have important cardiovascular actions. Histamine induces coronary vasoconstriction [26], (the histamine test has been replaced nowadays by the ergonovine test), induces tissue factor expression and activity [27] and activates platelets [28]. All three proteases, tryptase, chymase and cathepsin-D can activate matrix metalloproteinases, which can degrade the collagen cap and induce plaque erosion and rupture [29]. Tryptase exerts a dual action on the coagulation cascade with both thrombotic and fibrinolytic properties [30]. This action seems to depend on patient comorbidity and mast cell clonality. Indeed, it was found recently that activating mutations exist in *c-kit*, that codes for KIT, the receptor for stem cell factor which is essential for mast cell development, proliferation, survival, adhesion and homing [31]. This cascade of events results in a hyper responsive mast cell phenotype with increased release of mast cells tryptase able to more easily induce Kounis syndrome and differentiate mast cell content actions. Furthermore, chymase and cathepsin-D can act as converting enzymes and convert angiotensin I to angiotensin II, which is a major vasoconstricting substance [32]. Leukotrienes are also powerful vasoconstrictors [33] and thromboxane and PAF are platelet activators [34] with vasoconstricting properties [35].

There are three variants of Kounis syndrome. Type I variant includes patients with normal or nearly normal coronary arteries without predisposing factors for coronary artery disease in whom acute allergic attacks can induce either

coronary artery spasm alone without raised cardiac enzymes and troponins or coronary artery spasm leading to acute myocardial infarction with raised cardiac enzymes and troponins [36].

Type II variant includes patients with culprit but quiescent pre-existing atheromatous disease in whom the acute allergic attacks can induce either coronary artery spasm, or plaque erosion or rupture manifesting as acute myocardial infarction [36].

In view of recent case reports and studies that have shown coincidence of hypersensitivity reactions following implantation of drug-eluting stents and stent thrombosis which may be considered as a manifestation of Kounis syndrome, a type III variant of Kounis syndrome has been introduced [37]. This variant includes patients with stent thrombosis in whom thrombus harvesting and staining with hematoxylin–eosin and Giemsa reveals the presence of eosinophils and mast cells respectively in the pathology specimens.

Causes of Kounis syndrome

Experimental and clinical evidence indicates that the human heart can be the primary site and the target of anaphylaxis, resulting in the development of Kounis syndrome.

In experimental anaphylaxis with ovalbumin sensitized guinea pigs it was shown that within 3 min after the antigen administration cardiac indices were changed as follows [38]:

- Cardiac output decreased by 90%;
- Left ventricular end diastolic pressure increased significantly by 35%, indicating pump failure;
- Arterial blood pressure increased significantly by 35%. The blood pressure started declining steadily after 4 min.

Concurrently, electrocardiographic changes showed signs of acute myocardial ischemia. It was 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” [38].

Other *in vitro* studies in sensitized isolated and perfused heart have shown that the allergic reaction induces a marked coronary constriction with sustained impairment of cardiac contractility and a rapid decrease in coronary flow rates [39].

In a clinical study 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 pretreatment with cimetidine to antagonize H₂ receptors, two of the five patients (40%) developed angina during histamine infusion, accompanied by ST-T elevation, decrease coronary blood flow, increase coronary vascular resistance but with no significant changes in the mean arterial blood pressure [40]. In one of these two patients,

circumflex coronary arterial spasm was angiographically demonstrated during histamine-induced angina, which suggests that stimulation of the H₁ receptor induces a reduction of coronary blood flow either from vasodilation of small coronary resistance vessels or from stimulation of vasoconstricting H₁ receptors of large epicardial coronary arteries.

These findings oppose the belief that myocardial ischemia and myocardial infarction occurring during an allergic episode manifesting as Kounis syndrome, are the result of coronary

Box 2. Causes capable of inducing Kounis syndrome.

Drugs

- Analgesics (e.g., aspirin and dipyrene)
- Anesthetics (e.g., etomidate, isoflurane, midazolam, propofol, remifentanyl, rocuronium bromide, succinylcholine, suxamethonium and trimethaphan)
- Antibiotics (e.g., ampicillin, ampicillin/sulactam, amoxicillin, amikacin, cefazolin, cefoxitin, cefuroxime, cephadrine, cinoxacin, lincomycin, penicillin, sulbactam/cefoperazone, piperacillin/tazobactam, trimethoprim-sulfamethoxazole, sulperazon and vancomycin)
- Anticoagulants (e.g., heparin and lepirudin)
- Antineoplastics (e.g., 5-fluorouracil, capecitabine, carboplatin, denileukin, interferons, paclitaxel and vinca alkaloids)
- Contrast media (e.g., lohexone, loxaglate, diatrizoate meglumine and sodium indigotindisulfonate)
- Glucocorticoids (e.g., β -methasone and hydrocortisone)
- Nonsteroidal anti-inflammatory drugs (e.g., alclofenac, diclofenac and naproxen)
- Proton pump inhibitors (e.g., lansoprazole)
- Skin disinfectants (e.g., chlorhexidine and povidone-iodine)
- Thrombolytics (e.g., streptokinase, tissue plasminogen activator and urokinase)
- Others (e.g., allopurinol, enalapril, esmolol, dextran, bupropion, fructose, insulin, iodine, protamine, tetanus antitoxin, glaphenine and mesalamine)

Conditions

- Angioedema
- Bronchial asthma
- Churg–Strauss syndrome
- Exercise-induced anaphylaxis
- Food allergy
- Hay fever
- Idiopathic anaphylaxis
- Intracoronary stenting
- Mastocytosis
- Nicotine
- Serum sickness
- Urticaria

Environmental exposures

- Grass cutting
- Hymenoptera stings
- Jellyfish stings
- Latex contact
- Millet allergy
- Poison ivy
- Shellfish eating
- Viper venom

hypoperfusion due to systemic vasodilation, reduced venous return, leakage of plasma and volume loss from increased vascular permeability and depression of cardiac output [41].

In the everyday practice, a variety of causes have been reported as capable to induce Kounis syndrome. These include drugs, environmental exposures and several conditions (Box 2). Hymenoptera stings as well as other causes included in this table are common and could potentially become very dangerous.

For example, by pushing a single ant against the ventral forearm of 21 healthy volunteers, allowing it to sting for 60 s, two of the subjects (9.5%) developed chest pain with electrocardiographic changes suggesting acute myocardial ischemia [42]. Atopic individuals, as well as physicians, should be aware of this dangerous association.

Symptoms & signs of Kounis syndrome

The main clinical symptoms and signs of Kounis syndrome are always associated with subclinical, clinical, acute or chronic allergic reactions accompanied by cardiac symptomatology. These symptoms and signs are accompanied by electrocardiographic changes (Box 3). A high index of suspicion regarding this syndrome is of paramount importance. Although it is not a rare disease its diagnosis is easily overlooked [43]. Kounis syndrome cases, although under reported, are more often encountered in clinical practice and it is anticipated that many more causative factors will be implicated in the future. In the district of Achaia, Greece with a population of 300,000 inhabitants, 20 cases of Kounis syndrome have been encountered in the last 2 years caused by environmental exposures, drug allergies and stent implantation. Kounis syndrome has mostly been reported in southeastern Europe, especially Greece and Turkey. This geographical variation could be attributed to the following reasons: 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.

In any case of acute coronary syndrome, careful patient questioning may reveal a mechanism involving mast cell activation to precede the event. Routine cardiac evaluation for myocardial injury biomarkers, such as cardiac enzymes including CPK-MB and troponins, together with histamine and tryptase levels should be undertaken in any

Box 3. Clinical symptoms and signs together with their accompanying electrocardiographic changes.

Clinical symptoms

- Acute chest pain
- Chest discomfort
- Difficulty in swallowing
- Dyspnea
- Faintness
- Headache
- Malaise
- Nausea
- Pruritus
- Syncope
- Vomiting
- Urticaria

Clinical signs

- Bradycardia or tachycardia
- Cardiorespiratory arrest
- Cold extremities
- Diaphoresis
- Hypotension
- Pallor
- Palpitations
- Skin rash
- Sudden death
- Sweating

Electrocardiographic signs

- Atrial fibrillation
- Bigeminal rhythm
- Nodal rhythm
- Sinus bradycardia
- Sinus tachycardia
- ST segment depression or elevation
- T-wave flattening and/or inversion
- QRS complex prolongation
- QT segment prolongation
- Ventricular ectopics
- Ventricular fibrillation

patient with any grading of allergic reaction [44]. Chest symptoms, angina pectoris, recurrent myocardial infarction or sudden death in patients with stent implantation either in hospital or in the real world should also be considered as Kounis syndrome symptomatology [45].

Kounis syndrome: five typical cases of three Kounis syndrome variants

Case 1: centipede bite-induced type I Kounis syndrome

A 58 year old female physician with no previous cardiac or allergic history was bitten, while camping, by a dark brown centipede with yellow

extremities. Half an hour later she felt unwell and experienced extensive hand and arm edema with patchy areas of erythema. She went to the local hospital and while she was examined by the on-call physician she felt severe retrosternal pain, radiating to both arms and neck with vomiting and diaphoresis. An ECG showed ST-elevation in II, III and AVF leads compatible with inferior myocardial ischemia. She was then given steroids and antihistamine intravenously and her symptoms and signs gradually subsided. Cardiac enzymes and troponins were normal but peripheral blood examination showed eosinophils had increased to 8%. Subsequent echocardiography and coronary angiography revealed no abnormality.

Case 2: urticaria-induced type II Kounis syndrome

An 80 year old male smoker developed angioedema of the hands and generalized rash accompanied with severe itching. His previous history included hypercholesterolemia, and peripheral arterial disease with intermittent claudication. The symptoms had started 2 days previously and were treated by his physician with diphenhydramine. No specific etiological factors were detected. With this treatment his symptoms seemed to subside, but the third day, despite continuation of diphenhydramine, the symptoms worsened again and itching and erythema became more intense necessitating intravenous corticosteroid administration. However, he started complaining of chest pain radiating to the left arm neck, and left shoulder. He was brought to our hospital and an ECG showed Q wave and 1 mm ST-elevation in II, III and AVF leads. Cardiac enzymes, troponin and serum tryptase were elevated and eosinophils were 9%. Subsequent coronary angiography showed complete right coronary artery occlusion. The patient underwent angioplasty with stenting for type II variant of Kounis syndrome.

Case 3: contrast media-induced type II Kounis syndrome

A 50 year old obese woman with previous history of acute myocardial infarction was re-admitted because of episodes of recurrent mild chest pain and signs of myocardial ischemia on exercise testing. She did not give previous history of any allergic reaction or illness. She underwent coronary angiography, which showed 75% stenosis of left anterior descending coronary branch and 80% stenosis of the right coronary artery, for which she had angioplasty with stenting. During

the procedure she developed generalized maculopapular rash of the trunk and extremities, accompanied by intense pruritus, for which she was given intravenous antihistamines and corticosteroids. Half an hour later, while she was in the intensive care unit, she developed severe and constrictive retrosternal pain radiating to the neck and trunk. Electrocardiogram showed ST-elevation in the inferior leads and she again underwent angioplasty with thrombus aspiration from the stented right coronary artery. She was diagnosed as having type II variant of Kounis syndrome induced by the contrast agent in the stented artery.

Case 4: trimethoprim-sulfisoxazole-induced type II Kounis syndrome

A 77 year old hypertensive and diabetic male with previous history of myocardial infarctions was admitted due to complaining of feeling unwell and coughing. He was found to have bilateral lung ronchi and treatment was started with trimethoprim-sulfisoxazole. 1 hour after taking the first dose he started complaining of itching and developed generalized hives and severe retrosternal pain radiating to the neck and arms. The ECG showed elevation of ST segment in the precordial leads compatible with acute anterior myocardial infarction. Cardiac enzymes, troponin, eosinophils, IgE and tryptase were elevated. He was treated with the myocardial infarction protocol together with corticosteroids and antihistamines. An episode of atrial fibrillation was reverted to sinus rhythm with amiodarone. Subsequent coronary angiography revealed triple vessel disease and he was treated as having type II variant of Kounis syndrome with angioplasty and stenting.

Case 5: drug-eluting stent-induced type III Kounis syndrome

A 67 year old male, light smoker with a positive family history of coronary artery disease, initially underwent primary percutaneous coronary intervention in the right coronary artery (RCA) due to inferior ST-elevation myocardial infarction (STEMI), with implantation of two bare-metal stents 4 years before. After 1 year, a new coronary angiography due to a positive exercise test revealed restenosis of the proximal stent, therefore, placement of a paclitaxel-eluting stent was subsequently decided. Approximately 6 months later the patient was suffered from a new inferior STEMI and a new paclitaxel-eluting stent due to total occlusion just before the first stent. Subsequently, due to

positive thallium single photon emission computed tomography, a new coronary angiography revealed severe in-stent restenosis of RCA at the distal stent and a new biolimus-eluting stent was implanted. However, 2 months later the patient suffered a recurrent inferior STEMI and the RCA was totally occluded. An aspiration device was used and thrombus analysis revealed the existence of numerous eosinophils (FIGURE 1). Intravascular ultrasound did not show malapposed struts and dilatation with a noncompliant balloon and paclitaxel-eluting balloon was performed. The eosinophilic thrombus infiltration following repeated stent implantation was suggestive of a type III variant of Kounis syndrome. Different kinds of metals or drugs could be potential mechanisms of hypersensitivity leading to subacute stent thrombosis and/or stent restenosis.

Kounis syndrome during anesthesia

The anesthetized patient is under the influence of several factors that can induce allergic reaction and Kounis syndrome. Neuromuscular blocking drugs, antibiotics, latex exposure, contrast media, hypnotic agents, opioids, colloids, apronitin, protamine, chlorhexidine, dyes, local anesthetics and blood transfusion are some of

the offenders. Anaphylaxis from passive transfer of peanut allergen has also been described recently [46,47]. Anaphylaxis usually occurs shortly after induction but it may occur at any time with all potentially allergenic substances [48].

The clinical features mainly involve the cardiovascular system, manifesting as Kounis syndrome, but cutaneous or mucus involvement, and bronchospasm are also presenting features. According to Ring and Messmer the anaphylactic symptoms and signs are graded as grade I involving cutaneous-mucus signs, grade II involving mild cutaneous-mucus signs that may be combined with cardiorespiratory signs, grade III involving cutaneous-mucus signs and/or bronchospasm with cardiovascular collapse and grade IV denoting cardiac arrest [49]. The latter two grades correspond with the Kounis syndrome symptomatology.

The involvement of so many agents during anesthesia seems to be the cause of direct or IgE mediated mast cell degranulation. It is known that mast cell surfaces have between 500,000 and 1 million IgE molecules and degranulation occurs when 2000 of these molecules, which is a critical number, make 1000 bridges by antigens. These bridges can be made by antigens of different specificities as it happens in patients

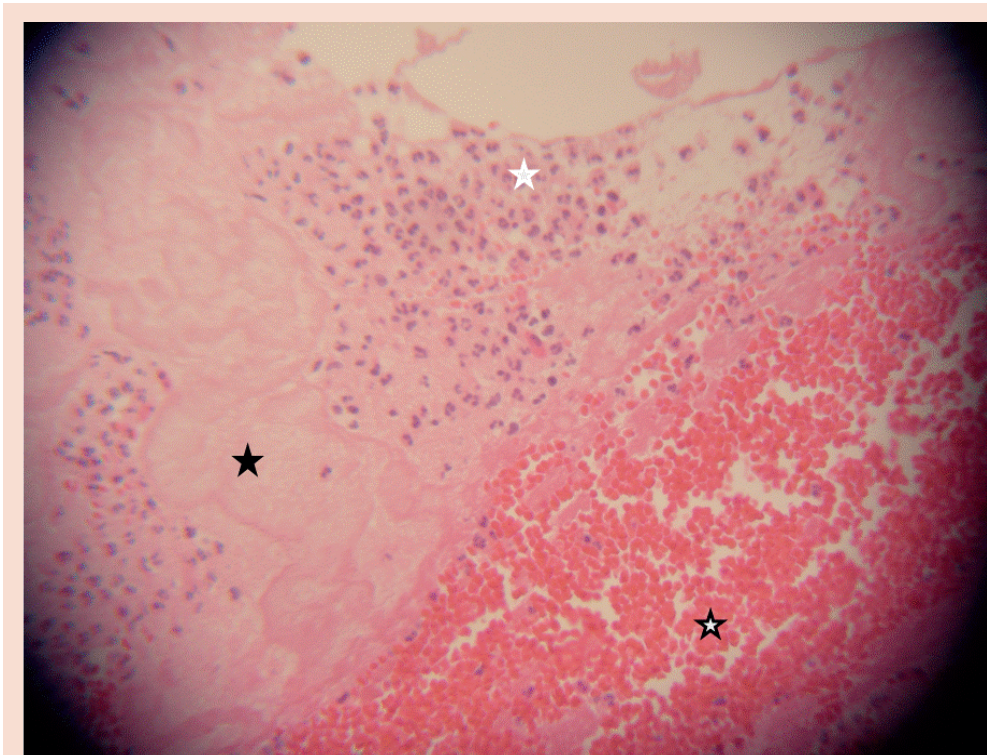


Figure 1. Aspirated thrombus from patient with type III variant of Kounis syndrome. White star shows thrombus infiltrated by numerous eosinophils, black star shows fibrin deposition and black-white star shows red cells mixed with scattered eosinophils.

during anesthesia [50]. It appears likely that the more antigens an anesthetized patient is exposed to, the easier and quicker the degranulation occurs [51–53].

Measuring of histamine, which has very short plasma half-life (8–10 min) [54] and tryptase which has an intermediate plasma half-life (90 min) [55], as well as measuring IgEs for thiopental, propofol, antibiotics, suxamethonium, quaternary (choline analog), ammonium (is thought to be the allergenic determinant in neuromuscular blocking drugs) together with prick tests followed by intradermal tests, can corroborate the diagnosis and identify the culprit cause of Kounis syndrome during anesthesia.

Kounis syndrome: hypersensitivity myocarditis or isolated eosinophilic coronary arteritis?

Kounis syndrome is a hypersensitivity-induced coronary syndrome that shares nearly identical symptomatology, cardiac manifestations and laboratory findings with another hypersensitivity cardiac disease called hypersensitivity myocarditis [56]. Hypersensitivity myocarditis is an inflammatory disease affecting the myocardial tissue and the cardiac conduction system manifesting mainly as a complication of drug therapy. The only differences between these two hypersensitivity conditions are that in hypersensitivity myocarditis there is presence of eosinophils, atypical lymphocytes and giant cells in myocardial biopsy, whereas biopsy in Kounis syndrome is typically normal. Furthermore, the coronary angiogram in hypersensitivity myocarditis is normal, whereas angiogram in Kounis syndrome, especially in type II variant, shows the presence of coronary artery disease. Mildly elevated cardiac enzymes and mild chest pain are characteristics of drug-induced myocarditis while eosinophilia may be absent in both conditions (TABLE 1). Hypersensitivity myocarditis can affect individuals of any age, but cases of Kounis syndrome have been reported in juveniles [57]. Physicians should be aware of the existence hypersensitivity myocarditis and Kounis syndrome, because they are not rare diseases, but are very rarely diagnosed and very difficult differentiated diseases.

Kounis syndrome can rarely complicate the Churg-Strauss syndrome (bronchial asthma, eosinophilia, vasculitis affecting medium and small-sized arteries and veins in a variety of organs) [58]. A cryptogenic form of isolated

eosinophilic arteritis leading to vasospastic angina, myocardial infarction, coronary artery dissection and sudden death seems to share the same pathophysiology with Kounis syndrome. This entity is characterized by eosinophilic infiltration of adventitia, media and intimal subendthelium together with diffusely distributed mast cells [59]. Eosinophils are bone marrow-derived granulocytic leukocytes, which normally reside in tissues and express H4 histamine receptors. These receptors facilitate eosinophil chemotaxis toward mast cells which are the major producers of an array of inflammatory soluble mediators which can induce Kounis syndrome. Soluble mediators secreted by mast cells and eosinophils modulate also reciprocal interactions between these two cells in the so called 'allergic effector unit' [60].

Kounis syndrome & coronary allograft vasculopathy

Vasculopathy of cardiac allografts is a progressive, accelerated and diffuse coronary artery disease affecting up to 50% of heart transplant recipients in the first 5 years and accounts for 40% of deaths more than 2 years after transplantation [61]. It is characterized by diffuse narrowing and occlusion of coronary arteries, while the conventional coronary disease shows more focal lesions. Muscle cells, macrophages, monocytes and T-lymphocytes are the type of cells involved in this process [62]. Immunologic mechanisms such as HLA mismatches, cytomegalovirus infection and nonimmunologic mechanisms such as endothelial injury, ischemia–reperfusion injury and classical factors for atherosclerotic coronary disease have been implicated. Although cellular and humoral alloimmunity are accepted pathogenic mediators, animal models suggest that T cells and Abs reactive to graft-expressed autoantigens, including cardiac myosin could also participate. However recent reports have associated coronary allograft vasculopathy with coronary artery spasm, myocardial infarction and even death [63].

Indeed, patients awaiting heart transplantation are receiving multiple drugs, including antibiotics and some of these drugs could have potentially triggered allergic responses.

In Gravanis series routine histological examination of the explanted hearts for heart transplantation revealed hypersensitivity myocardial involvement in 7% of patients [64]. In this series, the more drugs the patients were receiving pretransplantation, the higher absolute number of eosinophils was found in their blood. In

one patient who had received, while waiting for transplantation, 49 different medications, eosinophils were raised to 44%.

Based on the above reports and findings we have speculated that many of these medications could have acted as antigens or haptens (attached to body proteins) sensitizing the recipient's mast cells to produce corresponding IgE antibodies attached to the mast cell surface [65]. When, after heart transplantation, the patient is re-exposed to any of these potential antigenic agents, which now have corresponding IgE antibodies in mast cell membrane, then an intracoronary mast cell activation can occur in the transplanted heart. This will be followed by release of vasoconstricting and plaque eroding agents, which can induce coronary artery spasm, acute myocardial infarction manifesting as Kounis type I or type II syndrome variant or even death [63]. Therefore, in order to predict and treat coronary allograft vasculopathy we have recommended several tests and measures (Box 4) [64].

The brain, the heart & Kounis syndrome

A magnificent pathway seems to exist between the brain and heart culminating in mast cell activation and development of Kounis syndrome (FIGURE 2). Depressogenic stress impulses arising from high cortical centers of the brain are relayed through the limbic system to the hypothalamus [66]. In the hypothalamus, the paraventricular nucleus is activated by chemical mediators, which are released locally, such as norepinephrine, serotonin and acetylcholine and produce corticotropin-releasing hormone (CRH), which is the main coordinator of the depressogenic response. CRH enters the portal venous system of the hypothalamus and activates the corticotrophs of the anterior pituitary gland to produce proopiomelanocortin, which is cleaved to form adrenocorticotrophic hormone. It also stimulates the locus coeruleus, a dense collection of autonomic cells in the brainstem, to secrete norepinephrine at the sympathetic nerve endings.

The activation of the sympathetic system centrally is also transmitted peripherally to the adrenal medulla to produce large amounts of epinephrine. Adrenocorticotrophic hormone stimulates the adrenal cortex to produce corticosteroids. The sympathetic innervation of the kidney contributes in involvement of the renin-angiotensin system in this cascade.

These events result in heightened cardiovascular activity, endothelial injury, myocardial damage,

Table 1. Cardiac features of suspected hypersensitivity myocarditis and hypersensitivity coronary syndrome (Kounis syndrome).

	Kounis syndrome	Hypersensitivity myocarditis
Cardiac symptoms		
Acute chest pain	+	-
Chest discomfort	+	+
Dyspnea	+	+
Palpitations	+	+
Sudden death	+	+
Cardiac signs		
Elevated JVP	+	+
Irregular pulse	+	+
Gallop rhythm	+	+
Electrocardiographic signs		
Atrioventricular block	+	+
Left bundle branch block	+	+
Right bundle branch block	+	+
Sinus tachycardia	+	+
ST segment elevation	+	+
ST segment depression	+	+
T-wave inversion	+	+
Ventricular tachycardia	+	+
Laboratory signs		
Coronary angiography	+/-	-
Eosinophilia	+/-	+/-
Increased cardiac enzymes and especially CPK-MB	+	+
Increased troponins	+	+
Cardiomegaly in the chest X-ray	+/-	+/-
Dilated cardiac chambers in echogram	+/-	+/-
Eosinophils, atypical lymphocytes and giant cells in biopsy	-	+
AMA (indium 111)	-	+
MRI: subendocardial gadolinium concentration	+	-
MRI: subepicardial gadolinium concentration	-	+

+ : Present; - : Not present; +/- : Might or might not be present; AMA: Antimyocin monoclonal antibodies; JVP: Jugular venus pressure.

induction of adhesion molecules on the endothelial cells to which recruited inflammatory cells adhere and translocate to the arterial wall [67]. An acute phase response, similar to that associated with inflammation, is also engendered, and is characterized by mast cell and macrophage activation, resulting in the release of cytokines including IL-1, IL-6, TNF- α and acute phase proteins able to induce Kounis syndrome.

On the other hand, the same cytokines such as IL-1, IL-6, TNF- α , are released in patients with myocardial infarction and congestive cardiac

failure and play a mediating role in the genesis of depression following these conditions [68]. Experimentally, mast cell degranulation can be induced by immobilization stress in rat cardiac mast cells and this can be inhibited by pretreatment with mast cell stabilizer sodium cromoglycate and blocked locally by preincubation with antiserum against CRH and CRH type-1 receptor selective antagonist [69].

Kounis & Takotsubo syndrome

Takotsubo syndrome, also known as apical ballooning syndrome, takotsubo cardiomyopathy, stress-induced cardiomyopathy, broken heart syndrome, apical ballooning syndrome or transient LV dysfunction syndrome (named from a Japanese pot for catching octopus – like the appearance of the heart on left ventriculography), is a clinical condition affecting individuals (mainly women), associated with emotional distress, resembling acute myocardial infarction, but usually with normal coronary arteries and transient left ventricular dysfunction. Many questions regarding etiology, pathophysiology and treatment remain unanswered. There are several reports associating Takotsubo syndrome with Kounis syndrome [70–73] and patients not only suffering from anaphylaxis [74] but individuals simply observing and assisting in the treatment of anaphylaxis-induced Takotsubo syndrome [75].

It has been suggested that simultaneous multi-vessel coronary spasm at the epicardial artery or microvascular levels may contribute to the onset of this type of cardiomyopathy. Therefore, coronary artery spasm by anaphylactic mediators may initiate stress induced cardiomyopathy during anaphylactic reactions [76].

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 [77].

Catecholamine increase, with excessive activation of cardiac catecholamine receptors in the left ventricle, plays a major role in the pathophysiology of stress-induced cardiomyopathy [78,79]. In addition to this phenomenon, administration of catecholamines, such as epinephrine and norepinephrine, for hemodynamic support of anaphylactic shock would also increase the plasma catecholamine level. It is possible that the increased catecholamine levels during anaphylaxis may provoke stress induced cardiomyopathy.

The release of various cytokines has been also demonstrated to induce it. Since anaphylactic reaction can also induce it, the measurement of inflammatory mediators such as histamine, neutral proteases, and arachidonic acid products or the use of corticosteroids or mast cell stabilizers for prevention and treatment may shed light on its etiology and pathophysiology.

Box 4. Laboratory tests and measures in both donor and recipient in order to predict and treat coronary allograft vasculopathy.

- Careful history of drug and adverse drug reactions and allergies
- Both antibody and skin testing when and where appropriate
- Macrophage and T-cell activation studies
- Measuring of acute phase reactants
- Desensitization strategies if it is proved necessary
- Histological examination for allergic myocarditis in both donor and recipient hearts
- Considering the use of mast cell stabilizers in association to steroids and immunosuppressants
- Monitoring of the following inflammatory mediators:
 - Total IgE
 - Specific IgE to drugs received and receiving by donor and recipient
 - Chymase
 - Trypsin
 - Histamine
 - Arachidonic acid products (e.g., thromboxane, leukotrienes and prostaglandins)
 - C-reactive protein (high sensitivity)
 - Tissue factor
 - TNF
 - INF
 - IL-6, IL-2, IL-18, IL-10 (with anti-inflammatory activity)

Kounis syndrome & stent thrombosis

In order to induce an allergic reaction and consequently Kounis syndrome, the presence of allergens is essential and such a presence takes place throughout the stenting process. The first generation drug-eluting stents are composed from a metal strut, which is made from stainless steel containing nickel, chromium, manganese, titanium and molybdenum, the polymer coating and the eluted drug, which for the TAXUS stent is the antineoplastic paclitaxel and for the CYPHER stent is the antiproliferative agent rapamycin [80]. All these 3 components are strong allergens and constitute an allergic complex inside the coronaries. Nickel can induce a variety of allergic reactions including the baboon syndrome [81]. Similar allergic reactions can be induced by the polymer coating and the eluted drugs [81]. The second generation drug-eluting stents, which have the misleading title 'cobalt chromium stents' also contain nickel and other metals [82]. The XIENCE (everolimus stent) stent contains approximately

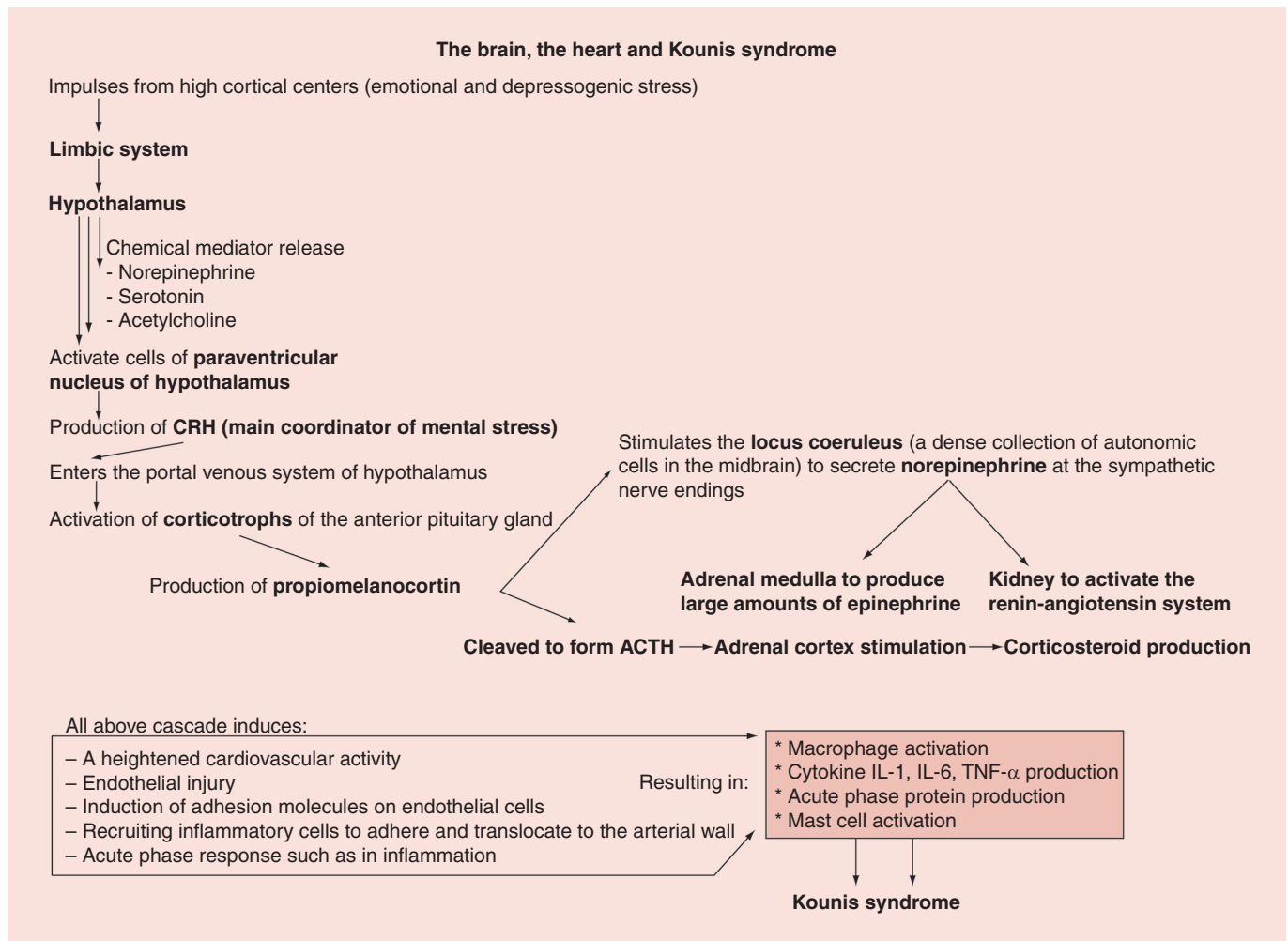


Figure 2. Shows how impulses from high cortical centers after emotional and depressogenic stress, via a cascade of actions, stimulations, secretions and interactions, can lead to the development of Kounis syndrome.

ACTH: Adrenocorticotropin hormone; CRH: Corticotropin-releasing hormone.

10% nickel and the ENDEAVOR (zotarolimus stent) stent 35% nickel, more than the first generation stents.

The stented patients should take clopidogrel, a well known allergen, for 1, 2 or more years. These patients should take also aspirin, which can also act as an allergen. Furthermore, atopic patients with stent implantation in the real world are exposed to any environmental exposure such as taking drugs or insect stings. Therefore, more than five antigens (perhaps six) can join forces in order to degranulate mast cells and release their mediators. We must emphasize that mast cell surface brings 500,000 to 1 million IgE molecules and degranulation occurs when 2000 of these molecules make 1000 bridges by antigens of different specificities as it happens in the stented patients [50].

Unexpected, bizarre, strange, astonishing and surprising reports have shown patients who developed stent thrombosis immediately

after an allergic reactions from other causes. For example, allergic reactions from propylphenazone [83], contrast material [84] and insect sting [85] were accompanied with intrastent thrombosis denoting that stents attract inflammatory cells like a magnet and constitute the area of possible mast cell and platelet activation.

Clinical, laboratory and animal studies have shown that stent thrombosis is the result of hypersensitivity inflammation.

In the first report concerning a patient with CYPHER stent who died from very late stent thrombosis, pathology revealed strut malapposition, aneurysmal dilatation and thrombus formation. Numerous eosinophils with T-lymphocytes, macrophages and giant cells were seen in the intima, media and adventitia [86].

Stent thrombosis, and thrombosis in general is the result of platelet adhesion, platelet activation and platelet aggregation [87]. Platelet

adhesion commences when shear forces induce extensions in the platelet membrane, known as tethers, which bind transiently to the injured endothelium in an 'on and off' and 'start and stop' fashion via interaction of the GP Ib receptor with von Willebrand factor (VWF). This process is called tethering and it is followed by platelet rolling, which is the result of interaction between GP VI receptor and collagen.

Platelet activation is taking place via stimulation of some known receptors in the platelet surface such as receptors for ADP, thromboxane, thrombin, serotonin, epinephrine and some less known receptors such as receptors for PAF, histamine and for high- and low-affinity IgE receptors which are known as FC ϵ RI and FC ϵ RII. During their activation platelets change shape from discoid to spiculated form and release granules that contain proinflammatory, prothrombotic, adhesive and aggregatory mediators.

The third and final stage of thrombosis is platelet aggregation. Platelet aggregation is the result of binding of GP IIb/IIIa receptor with fibrinogen and interaction with VWF. Thrombin converts fibrinogen to fibrin, which serves as a stable lattice for the creation of thrombus.

Therefore, receptors for hypersensitivity mediators are also involved in platelet activation and these mediators are derived from the allergic unit of eosinophils and mast cells [88].

This has been confirmed by several experiments, for example, in hamsters, Nemer *et al.* have managed to abrogate late thrombotic events induced by diesel particles by stabilizing mast cells with disodium cromoglycate or dexamethazone and this was attributed to the prevention of release of histamine from mast cells [89]. In other experiments, human blood platelets were stimulated with ADP in 3 experimental systems: whole human blood from healthy male donors, platelets in plasma and isolated platelets, but antihistamines inhibited platelet activation-aggregation [90,91].

Treatment of Kounis syndrome

Treatment of Kounis syndrome may be challenging because firstly, it needs to consider both cardiac and allergic symptoms simultaneously and secondly the drugs administered for these manifestations can worsen allergy and aggravate heart function [92].

Type I variant: in these patients treatment of the allergic event alone can abolish type I variant. The use of intravenous corticosteroids

such as hydrocortisone at a dose of 1–2mg/kg/day and H1 and H2 antihistamines such as diphenhydramine at a dose of 1 to 2 mg/kg and ranitidine at a dose of 1 mg/kg are appropriate.

Corticosteroids suppress the release of arachidonic acid from cell membrane and inhibit eicosanoid biosynthesis (via phospholipase A2 inhibition), induce cell apoptosis and reduce inflammation via up-regulation of death receptor CD95 and its ligand CD95L and induce synthesis of proteins called annexins (lipocortins), which modulate inflammatory cell activation, adhesion molecule expression and trans migratory and phagocytic functions.

In addition, vasodilators such as calcium-channel blockers and nitrates can abolish hypersensitivity induced vasospasm.

Type II variant: in these patients an acute coronary event protocol together with corticosteroids and antihistamines should be applied. Vasodilators such as nitrates and calcium blockers are given when appropriate.

Type III variant: in these patients the use of mast cell stabilizers in association with steroids and antihistamines should be recommended. Furthermore, harvesting of intrastent thrombus together with histological examination of aspirated material and staining for eosinophils (hematoxylin and eosin) and mast cells (Giemsa) should be undertaken. In patients who develop allergic symptoms following stent implantation desensitization measures should be applied.

One should bear in mind that:

- Nitroglycerin causes hypotension and tachycardia, which may further complicate allergic reaction;
- β -blockers can exaggerate coronary spasm due to unopposed action of α -adrenergic receptors;
- Epinephrine is the drug of choice and can save lives in anaphylaxis, but in Kounis syndrome can aggravate ischemia and worsen coronary vasospasm. However, in severe cases sulfite free epinephrine is preferable to be given intramuscularly because it has faster onset of action and more sustained levels as compared with the subcutaneous route (recommended intramuscular doses 0.2–0.5 mg [1:1000]). Aqueous solution is preferable;
- In patients with previous history of coronary heart disease who receive β -blockers epinephrine may be ineffective. It may also induce more vasospasm due to unopposed α -adrenergic effect. Glucagon may be considered;

- Opiates such as morphine, codeine and meperidine which are usually given to relieve acute chest pain from myocardial infarction should be administered with extreme caution in patients with Kounis syndrome, since they can induce massive mast cell degranulation and aggravate allergic reaction. Fentanyl and its derivatives show slight mast cell activation and should be the drugs of choice when narcotic analgesia is necessary.

Prognosis of Kounis syndrome

The prognosis of Kounis syndrome depends on the patient's comorbidity, sensitivity, the site of antibody–antigen reaction, the route of allergen entrance, the allergen concentration, the number of allergens the patient is exposed to and the magnitude of the initial allergic response [15,16]. In addition, the syndrome's variance plays an important role in the prognosis. For example, the type I variant, which includes patients without predisposing factors for coronary artery disease with normal or nearly normal coronary arteries, has better prognosis than the type II variant, which includes patients with pre-existing atheromatous coronary disease. However, in patients with the type III variant of Kounis syndrome, which includes patients with stent thrombosis with thrombus filled with eosinophils and mast cells, the prognosis is grave. In a recent report the rate of stent thrombosis was 4.4% after 22 months (very late stent thrombosis) and the death rate 36% [93]. Since it is not known whether very late stent thrombosis is a time-limited phenomenon, the problem might increase, if events continue to accrue over time [94]. Furthermore, Kounis syndrome cases affecting the inferior myocardial wall have better prognosis than those affecting the anterior myocardial wall.

Following Kounis syndrome, death can occur from cardiac arrhythmias or pulmonary edema in the acute phase and from cardiac failure in a later phase [95].

Clinical & therapeutic implications of Kounis syndrome

Kounis syndrome is a ubiquitous disease affecting individuals of any age, which can complicate many conditions and explain many clinical conundrums [57,96,97]. We anticipate that more unexplained clinical vascular manifestations are based on Kounis syndrome pathophysiology. It has been stated that Kounis syndrome is

not a rare disease but is a rarely suspected and diagnosed clinical condition [98]. The clinical literature is replete with references associating cardiac involvement with allergic conditions. It is certain that every physician is aware of this magnificent natural paradigm.

Although, allergic episodes are common in everyday practice, only few patients develop chest pain with/or electrocardiographic changes during these episodes.

The ability to predict the risk of Kounis syndrome in patients with allergic episodes remains a challenging issue for the physician.

We had previously suggested that a threshold level of mast cell content (tryptase, chymase and so on) exists [15] above which it can provoke coronary artery spasm and/or plaque erosion or rupture. Furthermore, the magnitude of the initial allergic response, the patient's sensitivity, the patient's comorbidity, the site of antibody–antigen reaction, the allergen concentration and the route of allergen entrance could represent additional factors.

Indeed, recent reports show that patients with increased serum baseline tryptase are prone to developed immediate and severe hypersensitivity reaction to hymenoptera sting [99]. Such patients were found to have underlying clonal mast cell disorder, either systemic mastocytosis or monoclonal mast cell activation syndrome [100].

In these patients, bone marrow aspiration showed mast cell granulomas and spindle-shaped mast cells. Flow cytometric analysis of mast cells revealed mast cells expressing CD2 or CD25 on their surface and KIT mutation analysis showed KIT mutation at codon 816. KIT is the mast receptor for the stem cell factor that is essential for mast cell development, proliferation, survival, adhesion and homing. Therefore, patients with serum baseline tryptase greater than normal, might have KIT mutations that lower the stimulus threshold for anaphylaxis, and have hyperresponsive mast cell phenotype resulting in the development of Kounis syndrome. Research efforts on this matter are currently under progress [101].

Clinical reports have shown that the absolute number of eosinophils and the eosinophil/leukocyte ratio in the peripheral blood are significantly elevated in patients with coronary artery disease [102] and eosinophil counts and plasma fibrinogen could predict the severity of vasospastic angina pectoris [103]. Other reports suggest that coronary vasospasm

associated with eosinophilia responds poorly to conventional vasodilator treatment and while the risk of recurrent coronary events is high, the majority of patients respond to treatment which suppresses eosinophilia such as corticosteroids [104]. Eosinophils are bone marrow-derived granulocytic leukocytes, which normally reside in tissues and express H4 histamine receptors. These receptors facilitate eosinophil chemotaxis toward mast cells, which are the major producers of histamine. Both eosinophils and mast cells are important effector cells in the late phase allergic response and they have been implicated in the pathogenesis of allergic diseases. Eosinophils respond to histamine by changing cell shape, upregulation of adhesion molecules and chemotaxis, and these responses are mediated by the H4 receptor expressed on eosinophils [105].

On the other hand, common allergic symptoms such as rhinoconjunctivitis and wheezing are significantly associated with an increased risk of coronary artery disease [106] and inhaled corticosteroid use may reduce the risk of myocardial infarction in asthma patients, particularly those with more severe disease [107].

Evidence exists, that the same substances released from the same cells are present in both acute allergic episodes and acute coronary syndromes and there is a common pathway between allergic and nonallergic coronary syndromes.

In a recent study, it was found that both serum tryptase and chymase were higher in nonallergic patients with acute myocardial infarction and unstable angina pectoris than in patients without substantial coronary disease suggesting that these proteases are important biomarkers for atherosclerotic plaque vulnerability [108].

In another study, persistent tryptase elevation was detected in patients with nonallergic acute coronary syndromes with higher concentration in the ST segment depression group in the acute phase and at follow up [109]. It was postulated that tryptase levels may be a potential new marker characterizing the unstable plaque and may differentiate patients with distinct types of acute coronary syndromes.

Similar findings were observed in nonallergic patients with significant chronic coronary artery disease, in whom raised tryptase levels were the result of chronic low-grade inflammatory activity present in the atherosclerotic plaques [110]. The authors of this report proposed that tryptase estimations may emerge as a novel way of identifying asymptomatic patients

with coronary artery disease and could represent a new biomarker of therapeutic efficacy in these patients [110].

Cuculo *et al.* measured tryptase levels in eight patients with unstable angina immediately after the onset of chest pain and electrocardiographic signs of onset of ischemia and found fivefold increase after 5 min, tenfold increase after 15 and 60 min and twice as low as in the period free of chest pain [111]. However, in the same study, five patients suffering from variant angina and challenged with ergonovine-provoked ischemia, tryptase levels remained normal, suggesting that a primary yet unknown stimulus activates mast cells in patients suffering from episodes of unstable angina.

Histamine blood concentration was found in patients with acute coronary syndromes of nonallergic etiology to be more than twice than age- and sex-matched controls and this increased level of histamine was associated with enhanced oxidative stress [112].

Increased histamine levels were found in the great cardiac vein in eight of 11 patients suffering from attacks of variant angina but were not observed in the eight control patients. However, histamine levels were not elevated during or after acetylcholine-induced coronary artery spasm. In contrast, histamine levels were raised just prior to angina attacks in three patients. In the same group of patients high levels of histamine were observed even in the absence of ST-segment elevation [113].

In a more recent study it was found that histamine blood level was significantly higher in patients with various types of ischemic heart disease when compared with control normal subjects [114]. In this study the higher histamine levels were observed in the group with unstable angina and acute myocardial infarction.

The same applies to the other mast cell mediators. For example, arachidonic acid metabolites such as thromboxane and leukotrienes have been found at significantly higher levels in the systemic arterial circulation in the acute stage of nonallergic myocardial infarction than in circulation of normal controls [115].

Furthermore, thromboxane and leukotrienes were significantly higher in nonallergic patients with unstable angina than in patients with stable angina and in patients with nonischemic chest pain [116]. Stress test-induced myocardial ischemia in the stable angina patients was not accompanied by any change in leukotriene and thromboxane up to 6 days after positive exercise test. It was concluded that this can rule out a

role of ischemia in the induction of increased eicosanoid products but the ischemia *per se* was induced by arachidonic acid products.

Finally, various studies have shown that interleukin-6 levels, derived from inflamed coronary plaques and areas of myocardial necrosis, are elevated in patients with nonallergic acute coronary syndromes [117,118].

All of the above evidence supports the notion that drugs including mediator antagonists, inhibitors of mediator biosynthesis, leukotriene antagonists, mediator receptor blockers such as sodium nedocromil, sodium cromoglycate, ketotifen, lodoxamide, humanized IgG1 monoclonal antibodies and others which interfere with mast cell stabilization (Box 5) and prevent the release of mast cell contents, could emerge as novel therapeutic modalities capable of preventing acute coronary and cerebrovascular events. It has been stated that “a new possibility emerges for the prevention of the progression of coronary plaques to unstable lesions, and that is; inhibition of mast cell degranulation” [119]. This has already been achieved experimentally when late thrombotic events were abrogated by stabilizing mast cell membrane with sodium cromoglycate and reducing inflammation with dexamethasone [89].

Conclusion

Kounis syndrome is ubiquitous disease representing a magnificent natural paradigm and nature's own experiment in a final trigger pathway implicated in cases of coronary artery spasm and plaque rupture. It has been stated that this syndrome might have profound clinical and therapeutic implications [120]. Stabilization of the mast cell membrane will inhibit mast cell degranulation and prevent acute coronary and cerebrovascular events, at least in some instances.

Future perspective

Mother nature is continuously performing natural experiments and has given to us, on several occasions, natural paradigms pointing the way towards discovering therapeutic and scientific modalities for the benefit of human race. In this concept, there are everyday paradigms associating cardiac involvement during hypersensitivity processes. The clinical literature abounds with reports associating chest discomfort, syncope, angina pectoris and myocardial infarction with hypersensitivity conditions. It is certain that practicing physicians and even patients during their everyday activities have come across such magnificent

Box 5. Drugs and natural molecules able to stabilize mast cells.

- IgG1 humanized monoclonal antibodies recognizing and masking corresponding IgEs in mast cell membrane
- Simultaneous inhibition of H1 and H2
- Lodoxamide
- Sodium nedocromil (Intal®)
- Sodium cromoglycate (iomuntal)
- Ketotifen-H1-blocker (Zaditen)
- Flavonoid quercetin
- Flavone luteolin inhibits T cells, mast cells and mast cell-dependent T-cell activation
- Relaxin (hormone from corpus luteus and prostate, generates nitric oxide)
- Nitric oxide which inhibits IL-6 production through TNF- α inhibition
- Peptides from C3 α , C3 α *, C3 α 9*, inhibit Fc ϵ RI-induced degranulation and TNF- α release
- Zaprinast (phosphodiesterase inhibitor)
- Stem cell factor targeting drugs, since stem cell factor is essential for mast cell development, proliferation, survival, adhesion and homing

natural paradigms. Recent clinical and experimental research has shown that mast cells are accumulated at the area of coronary artery spasm and plaque erosion or rupture in acute myocardial infarction patients. Inflammatory mediators released from mast cells, including the neutral proteases tryptase and chymase, histamine and arachidonic acid products, have found at increased levels in the blood or urine of patients suffering from acute coronary syndromes of allergic and nonallergic etiology. These mediators have been implicated in many clinical and experimental studies as inducing coronary artery spasm and/or acute myocardial infarction.

Kounis syndrome is the consequence of the above association. Stabilizing mast cells and preventing the release of such mediators could emerge as a novel therapeutic measure in our effort to prevent the number one devastating disease and cause of death of our time, namely acute coronary and cerebrovascular events. This evidence supports the notion that drugs, already existing in the human armamentarium and others that are currently used experimentally that interfere with mast cell stabilization and prevent the release of mast cell contents could emerge as novel therapeutic strategies capable of preventing acute coronary and cerebrovascular episodes. It seems that a new possibility emerges for the prevention of the progression of coronary plaques to unstable lesions culminating in acute myocardial infarction, and inhibition of mast cell degranulation. Experimentally, this has already been achieved when late thrombotic events were abrogated by

stabilizing mast cell membrane with sodium cromoglycate and reducing inflammation with dexamethasone. Future developments will demonstrate whether these encouraging

experiments, thoughts, ideas and wishes will be applied in everyday clinical practice. If so, then medicine will have achieved a triumph against this so feared contemporary plight.

Executive summary

Pathophysiology

- The human heart seems to be the primary target of anaphylaxis because minutes after the insult, left ventricular end diastolic pressure increases significantly indicating pump failure, cardiac output decreases significantly and blood pressure decreases after an initial increase. Concurrently, electrocardiographic signs of acute myocardial ischemia become evident.

Causality

- Myocardial ischemia and myocardial infarction occurring during an allergic episode manifesting as Kounis syndrome, does not seem to be the result of coronary hypoperfusion due to systemic vasodilation, reduced venous return, leakage of plasma and volume loss from increased vascular permeability and depression of cardiac output.

Clinical manifestation

- In any case of acute coronary syndrome, careful patient interrogation for atopy, allergies and hypersensitivities may reveal a mechanism involving mast cell activation preceding the event. Routine cardiac evaluation for myocardial injury biomarkers such as cardiac enzymes and troponins, together with tryptase and if possible histamine levels should be undertaken in any patient with any grading of allergic reaction.

Anesthesia & Kounis syndrome

- In anesthesia, many agents are involved including neuromuscular blocking drugs, antibiotics, latex, contrast media, hypnotic agents, opioids, colloids, apronitin, protamine, chlorhexidine, dyes, local anesthetics and blood transfusions which can cause direct or immunoglobulin mediated mast cell degranulation. It appears likely that the more drugs and agents an anesthetized patient is exposed to, the easier and quicker the mast cell degranulation occurs.

Kounis syndrome & hypersensitivity myocarditis

- In hypersensitivity myocarditis there is presence of eosinophils, atypical lymphocytes, and giant cells in myocardial biopsy but the coronary angiogram is normal. In Kounis syndrome, myocardial biopsy is typically normal but coronary angiogram, especially in type II variant, shows coronary artery disease with coronary stenosis. In eosinophilic arteritis, vasospastic angina, myocardial infarction, coronary artery dissection and sudden death appears to share the same pathophysiology with Kounis syndrome.

The brain, the heart & Kounis syndrome

- The existing pathway between the brain and heart culminating in mast cell activation and the development of Kounis syndrome includes: depressogenic stress impulses arising from high cortical centers, hypothalamus, paraventricular nucleus to release norepinephrine, serotonin, acetylcholine and corticotropin-releasing hormone. The activation of the sympathetic system centrally is also transmitted peripherally to the adrenal medulla and increases the amounts of epinephrine. Adrenocorticotrophic hormone stimulates the adrenal cortex to produce corticosteroids. The sympathetic innervation of kidney contributes in involvement of the rennin–angiotensin system in this cascade of actions, stimulations, secretions and interactions, which can lead to the development of Kounis syndrome.

Takotsubo & Kounis syndrome

- Anaphylactic reactions can also induce Takotsubo syndrome, therefore the measurement of inflammatory mediators such as histamine, neutral proteases and arachidonic acid products, or the use of corticosteroids or mast cell stabilizers for prevention and treatment may shed light on the etiology and pathophysiology of Takotsubo syndrome.

Stent thrombosis & Kounis syndrome

- Stent components include the metal strut made from stainless steel containing nickel, chromium, manganese, titanium and molybdenum, the polymer coating and the eluted drugs. The stented patients also take aspirin and clopidogrel and are exposed to the environment. These six elements act as antigens and can induce intracoronary mast cell degranulation culminating in Kounis syndrome and stent thrombosis. Information sheets inside the commercial stent packages state this and warn about the possibility of Kounis syndrome.

Therapeutic points

- In Kounis syndrome, nitroglycerin can worsen hypotension, β -blockade can exaggerate coronary spasm, epinephrine can aggravate ischemia, worsen coronary vasospasm, promote platelet aggregation, increase thromboxane B₂ production and due to its sulfite content, can induce anaphylaxis. Therefore, sulfite free epinephrine is preferable. Opiates can induce massive mast cell degranulation and aggravate allergic reaction, whereas fentanyl and its derivatives show slight mast cell activation and should be the drugs of choice when narcotic analgesia is necessary.

Conclusion

- New possibilities continue to emerge for the prevention of the progression of coronary plaques to unstable lesions and acute coronary syndromes and that is; inhibition of mast cell degranulation. This has already been achieved experimentally when late thrombotic events have been abrogated by stabilizing mast cell membrane with sodium cromoglycate and reducing inflammation with dexamethasone. It is up to clinicians to corroborate this.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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