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Editorial

Kounis Syndrome or Allergic Angina: An Elusive Entity

THE ADVENT AND EVOLUTION of cardiothoracic anesthesia has allowed for an increased number of patients, often with complex cardiovascular diseases, to undergo noncardiac and cardiac surgery with overall improved outcomes and safety.^{1,2} Preoperative noninvasive cardiovascular imaging has improved risk stratification and led to better surgical preparedness and participation of trained cardiovascular anesthesiologists when deemed necessary.

In this issue of the *Journal of Cardiothoracic and Vascular Anesthesiology*, Dai et al. reported findings of the perioperative cardiovascular manifestations of Kounis syndrome.³ Among 35 case reports yielded in a systematic way, perioperative Kounis syndrome occurred predominantly in male patients aged 40-to-80 years old, and in the context of antibiotic use (12 patients; cephalosporins or fluoroquinolones) or paralyzing agents (6 patients; rocuronium or cisatracurium). Hemodynamic instability occurred on an average of about 20 minutes after the offending agent, although delayed presentation also was reported. Coronary angiograms revealed either vasospasm or no coronary disease. Supportive treatment for hemodynamic instability requiring vasoactive medications, antiarrhythmics, and defibrillation was the mainstay of treatment. Few cases reported use of antiplatelet (8 patients) and antithrombotic medication (5 patients) in addition to revascularization (4 patients). In rare circumstances, mechanical circulatory support was used (7 patients). Overall prognosis was favorable, with one death secondary to infectious complications reported among 35 patients.

The association of anaphylaxis and cardiovascular symptoms long has been reported.⁴ However, it was not until 1991 that the term “vasospastic angina” was used to describe the occurrence of coronary vasospasm and/or acute coronary syndrome in the setting of an allergic and hypersensitivity event with anaphylactic symptoms.⁵ Currently, 3 types have been described in the literature. Type 1 is related to coronary vasospasm in the setting of normal coronaries, type 2 with a vasospastic event in the setting of an underlying quiescent atheromatous plaque, and type 3 with coronary stent thrombosis containing an eosinophil-rich thrombus. Central to the pathophysiology of the syndrome is the release of systemic

inflammatory markers, such as histamine, cytokines, and growth factors, orchestrated by mast cells after interaction with an offending agent (Fig 1).⁶ The latter leads to a histamine-induced coronary vasospasm and the priming of prothrombotic events. Progression to acute coronary syndromes, with myocardial damage and the release of enzymes, not always is present but may occur.

Despite the presence of some common features, allergic angina should not be confused with the more common vasospastic angina, also known as “Prinzmetal angina”. Patients with vasospastic angina tend to be younger in age, more commonly women, frequently heavy smokers with symptoms occurring usually at rest, and manifesting with extremely severe angina that usually clusters between midnight and 8 AM.⁷ Vasospastic angina occasionally can develop in association with aspirin-induced asthma and use of 5-fluorouracil and cyclophosphamide. The ergot derivatives used to treat migraine headaches and serotonin antagonists used to treat depression can precipitate episodes of vasospastic angina.⁷

The perioperative diagnosis and management of Kounis syndrome can present challenges for the operative team. It is plausible that the diagnosis may remain elusive given the resemblance to other more common conditions. Ischemic and arrhythmic events commonly occur during anesthesia induction due to hypotension and hemodynamic changes, and can lead to worse outcomes.⁸ The presence of coronary artery disease in the setting of hypotension and shifting intravascular volumes may accentuate these effects. The diagnosis of postoperative ischemia and infarctions are further confounded by the effect of analgesics, postoperative surgical pain, and hemodynamic demand mismatch origin.⁹ Thus, it is conceivable that the diagnosis of Kounis syndrome may be even more difficult to make under these circumstances. Improved awareness of the entity and of potential offending agents has improved diagnosis recognition. This is further supported by the fact that 13 of 35 cases reported by Dai et al. were in the years 2018 and 2019, implying increased identification, rather than rising incidence, of the syndrome.³

An important clue to the diagnosis is persistent hypotension that requires unexpectedly higher doses of vasopressor therapies

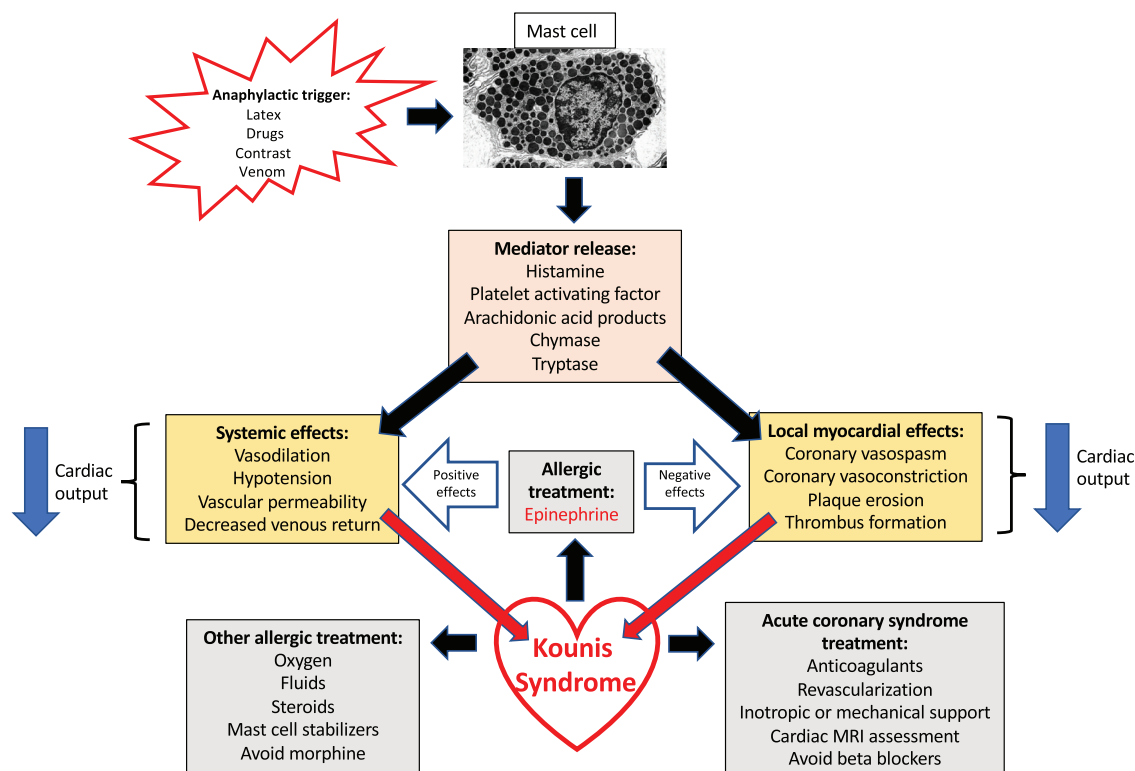


Fig 1. Graphic representation of the etiology and manifestations of Kounis syndrome or allergic angina.

due to the addition of anaphylactic shock to cardiogenic shock. Intraoperative transesophageal echocardiography may be helpful when available, and is likely to demonstrate numerous regional wall motion abnormalities due to diffuse vasospasm. However, the echo could also be normal in Kounis Syndrome. A “nonischemic”, noninvasive stress test, as recommended by guidelines, may decrease the likelihood of the diagnosis but does not completely exclude it.¹⁰ Normal coronary anatomy seen by means of angiography makes it much more likely to diagnose Kounis-related ischemia. Diagnosis of anaphylaxis during anesthesia can be achieved by measuring histamine (plasma half-life of 8-10 min), tryptase (half-life of 90 min), specific immunoglobulin E titers for thiopental, propofol, antibiotics, suxamethonium (choline analog), ammonium (thought to be the allergenic determinant in neuromuscular blocking drugs), and other given agents.¹¹ However, the practicality of this approach rightfully can be questioned. In most patients, Kounis syndrome will be a diagnosis of exclusion after angiography.

The management of the acute phase of the syndrome can be equally challenging. The co-existence of profound, persistent hypotension, along with signs of ischemia (eg, ventricular arrhythmias, ST elevation), may point to a cardiac origin of hemodynamic instability. The use of mechanical support in some of the case reports included in the manuscript could imply that cardiogenic dysfunction (in the setting of diffuse vasospasm) may be superimposed on the anaphylactic shock. Even if the condition is diagnosed correctly, the peripheral vasodilation requiring vasopressors, in conjunction with coronary vasospasm requiring vasodilators (eg, nitroglycerin,

calcium channel blockers), present a therapeutic oxymoron. Systemic vasodilators likely would lead to worse outcomes. In this context, coronary angiography also may have therapeutic implications. First, a percutaneous coronary intervention may be warranted in the case of acute thrombotic occlusion (type II or III), and second, intracoronary use of nitroglycerin may provide resolution of vasospasm while mitigating systemic vasodilator effects. These benefits, however, have to be weighed carefully against the administration of iodine contrast, an agent that potentially could worsen anaphylaxis.

In conclusion, Kounis syndrome is a rare entity that presents with diagnostic and therapeutic challenges in the perioperative period. Increased awareness and a high index of suspicion may improve recognition of the syndrome. More studies, similar to the one presented here by Dai et al., are needed to fully characterize the prevalence, demographics, and optimal management strategies for this syndrome.

Conflict of Interest

None.

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