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## LETTER TO THE EDITOR

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### TAKOTSUBO CARDIOMYOPATHY, ROCURONIUM ANAPHYLAXIS AND ANESTHESIA: THE ATAK COMPLEX IN GENERAL ANESTHESIA

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Takotsubo cardiomyopathy is a stress induced myocardial stunning. Stress generates impulses from high cortical centers via the limbic system of hypothalamus that activate subcortical structures to release neurohormones that can affect the cardiovascular system. However, despite continuous and laborious scientific efforts, the etiology, pathophysiology and treatment of Takotsubo cardiomyopathy is still elusive.

In the very interesting report published recently in *Middle East Journal of Anesthesiology*<sup>1</sup> a 44-year-old female patient smoker, on beta-blockade, allergic to penicillin and receiving phentermine for weight loss with laparoscopic banding for intentional weight loss, developed severe bronchospasm, without cutaneous manifestations, while she was operated for elective abdominal panniculectomy. The anesthetic medications were propofol, fentanyl and rocuronium. She was treated with continuous infusion of epinephrine and nebulized albuterol because her condition was not improving. Troponin levels were raised denoting myocardial damage and echocardiography showed severely decreased left ventricular systolic function with ejection fraction of 25% suspicious of mid cavitory variant Takotsubo cardiomyopathy. These findings were confirmed by coronary arteriography while the coronary arteries did not show any obstructive coronary artery disease. The suspected anaphylactic agent in this patient was rocuronium.

However, the patient was treated for non-ST-elevation myocardial infarction while electrocardiographic findings were not described and skin prick tests to the anesthetic drugs were not performed. The patient had a good recovery and was discharged home with a cardiology follow-up appointment and a referral to an allergy specialist.

**Keywords:** Anesthesia; Epinephrine; Kounis syndrome; Takotsubo cardiomyopathy; Anaphylaxis.

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This report is important because it shed light in etiology, pathophysiology and treatment of takotsubo cardiomyopathy, and the so called ATAK (Adrenaline, Takotsubo, Anaphylaxis, Kounis syndrome) complex<sup>2</sup>.

Adrenaline (epinephrine) and other mediators (serotonin, and acetylcholine) released from hypothalamus activate the paraventricular nucleus to produce corticotropin-releasing hormone which is the main coordinator of the stress response. This hormone activates the corticotrophs of the anterior pituitary gland to produce proopiomelanocortin which stimulates the locus coeruleus, a dense collection of autonomic cells in the brainstem, to secrete additional adrenaline at the sympathetic nerve endings. Such activation of the sympathetic system centrally is also transmitted to the adrenal medulla to produce even larger amounts of adrenaline. Consequently, the increased release of adrenaline induces excessive activation of cardiac catecholamine receptors in the left ventricle thus playing major role in pathophysiology of stress-induced cardiomyopathy. Furthermore, adrenaline administration for hemodynamic support, as in the described patient, would also increase the plasma catecholamines<sup>3</sup>.

Takotsubo cardiomyopathy is initiated by simultaneous multi-vessel coronary artery spasm at epicardial or microvascular levels. Such spasm can occur in association with various conditions, environmental exposures, drug administration, anaphylaxis and Kounis syndrome. Indeed, Takotsubo cardiomyopathy has been observed during perioperative anaphylaxis, mastocytosis, hymenoptera stings, anaphylaxis, adrenaline administration, pheochromocytoma crisis and not only in patients suffering from anaphylaxis but also in individuals simply observing and assisting in the treatment of anaphylaxis<sup>4</sup>.

Anaphylaxis is a condition in which catecholamines are released by the renin-angiotensin-aldosterone system together with histamine and both these substances stimulate the release of more catecholamine by direct action on the adrenal medullary cells. In a recent report measuring troponin levels and using echo-cardiographic techniques<sup>5</sup>, it was found that between 300 anaphylaxis cases

that were diagnosed in the emergency department, myocardial injury was developed in 7.3% of patients. Various cardiomyopathy, including Kounis syndrome and Takotsubo cardiomyopathy, was also observed in patients with increased troponin and myocardial injury.

Kounis syndrome is associated with anaphylactic mast cell and platelet activation from various causes and involves interrelated and interacting inflammatory cells. Following mast cell degranulation, several vasoconstricting and collagen-degrading compounds are released locally and in the peripheral circulation<sup>6</sup>. Apart from immunoglobulin E mechanisms, mast cells are activated also by cytokines, environmental exposures to pathogens and toxins, food, infections, drugs, and also mental stress<sup>7</sup>. In the described patient, despite that tryptase levels could not be determined because a second sample was sent only after more than 24hrs of suspected anaphylactic reaction, the troponin was elevated and the patient was treated as a non-ST-elevation myocardial infarction that denotes that a type I variant of Kounis syndrome was present<sup>8</sup>.

The described patient was allergic to penicillin and had received 3 anesthetic agents including fentanyl, propofol and rocuronium that could have acted as antigens with additive effects<sup>9</sup>. It is known that atopic patients simultaneously exposed to several drugs, acting as antigens, have more symptoms than do monosensitized individuals<sup>10</sup>. Furthermore, IgE antibodies with different specificities can have an additive effect and even small amounts of corresponding antigens can trigger mediator release when the patient is simultaneously exposed to them<sup>11</sup>.

All above show that anaphylactic mechanisms can induce Kounis syndrome, that anaphylactic reactions can induce stress cardiomyopathy and mental stress can induce mast cell and other interrelated inflammatory cell activation.

Therefore, measurement of inflammatory mediators such as histamine, neutral proteases, and arachidonic acid products and the use of mast cell stabilizers or corticosteroids for treatment and/or prevention of stress-induced cardiomyopathy may shed further light on the etiology, pathophysiology and treatment of Takotsubo cardiomyopathy.

## References

1. ALSHAERI T, GUPTA D, NAGABHUSHANA A: Peri-anesthesia anaphylaxis (paa): we still have not started post-paa testing for inciting anesthesia-related allergens. *Middle East J Anaesthesiol*; 23: 465-9, 2016.
2. CHENG TO, KOUNIS NG: Takotsubo cardiomyopathy, mental stress and the Kounis syndrome. *Int J Cardiol*; 161: 65-7, 2012.
3. LITVINOV IV, KOTOWYCZ MA, WASSMANN S: Iatrogenic epinephrine-induced reverse takotsubo cardiomyopathy: direct evidence supporting the role of catecholamines in the pathophysiology of the 'broken heart syndrome'. *Clin Res Cardiol*; 98:457-62, 2009.
4. JELLIS C, HUNTER A, WHITBOURN R, MACISAAC A: Tako-tsubo cardiomyopathy after observing anaphylaxis. *Intern Med J*; 39:630-1, 2009.
5. CHA YS, KIM H, BANG MH, KIM OH, KIM HI, CHA K, LEE KH, HWANG SO: Evaluation of myocardial injury through serum troponin I and echocardiography in anaphylaxis. *Am J Emerg Med*; 34:140-4, 2016.
6. KOUNIS NG: Kounis syndrome: an update on epidemiology, pathogenesis, diagnosis and therapeutic management. *Clin Chem Lab Med*; 54:1545-59, 2016.
7. PETRA AI, PANAGIOTIDOU S, STEWART JM, CONTI P, THEOHARIDES TC: Spectrum of mast cell activation disorders. *Expert Rev Clin Immunol*; 10:729-39, 2014.
8. SOUFRAS GD, LIANAS D, PATSOURAS N, TSIGKAS G, KOUNIS NG: Kounis syndrome: Aspects on pathophysiology and management. *Eur J Intern Med*; 32:e30-1, 2016.
9. KOUNIS NG, MAZARAKIS A, ALMPANIS G, GKOUIAS K, KOUNIS GN, TSIGKAS G: The more allergens an atopic patient is exposed to, the easier and quicker anaphylactic shock and Kounis syndrome appear: Clinical and therapeutic paradoxes. *J Nat Sci Biol Med*; 5:240-4, 2014.
10. SIMPSON A, SODERSTROM L, AHLSTEDT S, MURRAY CS, WOODCOCK A, CUSTOVIC A: IgE antibody quantification and the probability of wheezing in preschool children. *J Allergy Clin Immunol*; 116:744-9, 2005.
11. NOPP A, JOHANSSON SG, LUNDBERG M, OMAN H: Simultaneous exposure of several allergens has an additive effect on multisensitized basophils. *Allergy*; 61:1366-8, 2006.

