



# Attack the ATAK; A Challenging Contemporary Complex: Pathophysiologic, Therapeutic, and Preventive Considerations

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The adrenaline, takotsubo, anaphylaxis, and Kounis (ATAK) complex constitutes a challenging contemporary clinicopharmacological combination of syndrome ATAK.<sup>1</sup> “Attacking” is needed to elucidate its etiology and pathophysiology and implement preventive and therapeutic measures. Adrenaline is considered the drug of choice for anaphylactic shock; however, its administration, especially in excess doses, could contribute to coronary spasms. Moreover, coronary spasms through direct myocardial stunning can lead to Takotsubo syndrome (TS).<sup>2</sup> During anaphylaxis, the released mediators can also initiate coronary spasms and again TS.<sup>3</sup> Adrenaline administration as hemodynamic support during anaphylactic shock could also increase the plasma catecholamine levels and perpetuate this vicious cycle. Kounis syndrome has also been associated with TS.<sup>4</sup>

## Adrenaline

Paradoxically, adrenaline, the drug of choice for anaphylaxis, can induce anaphylaxis by itself. Indeed, commercially available adrenaline contains sodium metabisulfite as a preservative.<sup>5</sup> Anaphylactic reactions secondary to exposure to sulfites found in sparkling water have already been reported.<sup>6</sup> This situation poses a therapeutic dilemma in sulfite-sensitive patients who suffer from anaphylactic shock.<sup>7</sup> Fortunately, free sulfite adrenaline is currently commercially available for administration to patients with sulfite sensitivity (American Regent Inc., USA).

Glucagon is another alternative used successfully for anaphylaxis treatment in patients taking  $\beta$ -blockers.<sup>5,8</sup>

Interestingly, both the appropriate intramuscular adrenaline dose of 0.01 mg/kg of a 1:1,000 (1 mg/mL) solution to a maximum dose

of 0.5 mg in adults<sup>5,9</sup> and the appropriately diluted intravenous dose (1:10,000 [0.1 mg/mL] or 1:100,000 [0.01 mg/mL]) may also contribute to coronary spasms.

Adrenaline actions can be classified as follows:<sup>5,8</sup>

1. Actions via  $\alpha_1$  receptors can induce peripheral vasoconstriction,
2. Actions via  $\beta_1$  receptors can increase the rate and force of cardiac contractions,
3. Actions via  $\beta_2$  receptors can reverse bronchoconstriction and reduce the release of inflammatory mediators,
4. Promotes platelet activation via specific receptors found on the platelet surface,
5. Induces platelet aggregation by increasing the platelet production of thromboxane
6. Enhances platelet sensitivity to adenosine diphosphate,
7. Promotes thrombin-induced binding of platelets to fibrinogen and therefore aggravates myocardial ischemia, prolongs QTc intervals, and induces coronary vasospasms and arrhythmias. Both  $\alpha$ - ( $\alpha_1$ - and  $\alpha_2$ -) and  $\beta_1$ -adrenergic receptors are present in the coronary arteries but with different distributions.

Large coronary arteries are equipped mainly with  $\alpha$  receptors, which mediate contractions. Therefore, adrenaline may cause coronary vasoconstriction, reduce coronary blood flow, increase myocardial oxygen demand, worsen myocardial ischemia, and induce Kounis syndrome.<sup>9</sup>

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## Takotsubo (蛸壺 in Japanese) Syndrome

TS is referred to the medical literature with various names such as TS, stress-induced cardiomyopathy, takotsubo cardiomyopathy, apical ballooning syndrome, transient left ventricular apical ballooning, atypical apical ballooning, ampulla cardiomyopathy, broken heart syndrome, or transient left ventricular dysfunction syndrome. It was named after a round-bottomed and narrow-necked fishing pot-takotsubo in Japanese for trapping octopus because of its resemblance to the performed left ventriculogram.<sup>10,11</sup> Current international experts agree<sup>11</sup> about the common terminology of TS, although some aspects remain to be elucidated.<sup>12</sup>

TS has been reported during any catecholaminergic distress, acute neurogenic diseases, adrenaline administration, anaphylaxis, perioperative anaphylaxis, Kounis syndrome, mastocytosis, hymenoptera stings, pheochromocytoma crisis, and even in predisposed persons watching and assisting in the treatment of anaphylaxis.

The association of pheochromocytoma with TS and the surge of catecholamine released during pheochromocytoma adrenergic crisis appears to be the “Lydia lithos” (touchstone) for the elucidation of the pathophysiology of this syndrome.<sup>13</sup>

Indeed, TS is a clinical condition following emotional distress and affects individuals (mainly postmenopausal women), resembling acute myocardial infarction, with usually normal coronary arteries on coronary angiography, and transient left ventricular dysfunction.<sup>14</sup> Psychological strain including anxiety, depression, traumatic life events, and environmental and behavioral factors such as heat and cold can worsen or precipitate coronary disease through the stimulation of coronary mast cells, leading to local inflammation.<sup>15</sup>

Stress induces impulses from high cortical centers of the brain that are relayed through the limbic system to the hypothalamus.<sup>16</sup> Chemical mediators such as norepinephrine, serotonin, and acetylcholine are released and activate cells of the paraventricular nucleus of the hypothalamus to produce corticotropin-releasing hormone (CRH).

CRH is the main mediator of the stress response that enters the portal venous system of the hypothalamus to activate the corticotrophs of the anterior pituitary gland to produce proopiomelanocortin. The latter is cleaved to form adrenocorticotrophic hormone and stimulates the locus coeruleus, a dense collection of autonomic cells in the brainstem, to secrete more norepinephrine at the sympathetic nerve endings.

Such an activation of the sympathetic system results in the stimulation of the adrenal cortex to produce corticosteroids and stimulation of the renin-angiotensin system. This entire cascade induces<sup>17</sup> a heightened cardiovascular activity leading to an acute phase response, with macrophage activation, production of cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor alpha, acute phase proteins, and mast cell activation that constitute the pathogenesis of Kounis syndrome (Figure 1).

Therefore, stress from various causes can precipitate via an adrenaline surge, TS, and cardiac disease through a release of inflammatory mediators, and Kounis syndrome.

## Anaphylaxis

Anaphylaxis means “no-prophylaxis,” “opposite protection,” or “against protection,” whereas prophylaxis in Greek means “protection.”

This life-threatening condition occurs after activation of mast cells and other inflammatory cells by the release of various anaphylaxis-implicated mediators<sup>18</sup> resembling cytokine storm molecules (Table 1).

Mast cells and other inflammatory cells can activate each other through multidirectional signals like a “ball of thread,” participating in an inflammatory vicious cycle. For instance, mast cells can induce macrophage activation and enhance T-cell activation, whereas mast cells might be activated by inducible macrophage protein 1a. In addition, CD169 macrophages can induce CD8 T-cell activation, which in turn may mediate mast cell activation and proliferation and regulate macrophage activity.

These pathways are characteristics of mast cells:<sup>19</sup>

- By allergen crosslinking allergen-specific immunoglobulin (Ig)E bound to high affinity Fc epsilon receptor 1.
- Non-IgE-mediated mast cell degranulation via anaphylatoxins including complement C1q, C3a C5a, and factor B. This complement pathway activation involves IL-5 and tryptase and is much more common than recognized in patients who develop renal failure or fatal cerebral events.
- By the low-affinity mas-related G protein-coupled receptor X2 (MRGPRX2) that may activate mast cells via non-Fcε receptors.
- By neuropeptides, including CRH, neurotensin, and substance P via high affinity receptors.

Surprisingly, in complement and MRGPRX2 direct mast cell activation, tryptase levels may not be elevated and specific IgEs may remain undetected, especially in a condition as serious as Kounis syndrome.

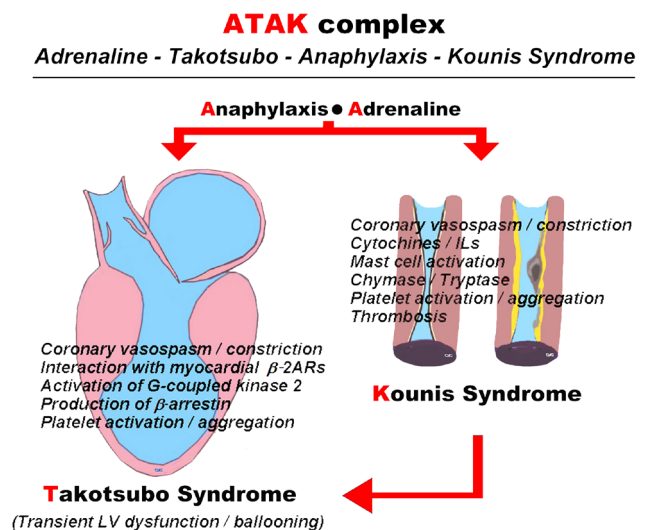


FIG. 1. The pathophysiology of the ATAK syndrome.

**TABLE 1.** Mediators of Anaphylaxis.

Preformed mediators	Newly synthesized mediators
<b>Biogenic amines</b>	<b>Complement breakdown products</b>
Angiotensin II	Anaphylatoxins C3a, C4a, C5a
Histamine	<b>Contact system activation products</b>
Renin	Bradykinin
Serotonin	<b>Cytokines</b>
<b>Chemokines</b>	Interleukins (IL)-1,2,3,4,5,6,9,10,13,16
IL-8, MCP-1, MCP-3, MCP-4,	Interferon- $\gamma$
RANTES	Macrophage activating factor
<b>Enzymes</b>	Tumor necrosis factor- $\alpha$
Arylsulfatases	<b>Lipid-derived mediators</b>
Carbopeptidase A	Leukotriene LT B4
Cathepsin G	Cysteinyl leukotrienes LTC4,
Chymase	LTD, TE4
Kinogenases	Platelet activating factor
Phospholipases	Prostaglandin D2
Tryptase	<b>Growth factors</b>
<b>Peptides</b>	Granulocyte monocyte-colony
Bradykinin	Stimulating factor
Corticotropin-releasing hormone	Fibroblast growth factor nerve growth factor
Endorphins	Stem cell factor
Endothelin	Vascular endothelial growth factor
Somatostatin	<b>Arachidonic acid products</b>
Substance B	Leukotrienes
Vasoactive intestinal peptide	Platelet activating factor
Urocortin	Prostaglandins (thromboxane)
Vascular endothelial growth factor Vascular factor	
<b>Proteoglycans</b>	
Chondroitin	
Heparin	
Hyaluronic acid	

IL, interleukin; MCP, monocyte chemotactic protein

### Kounis Syndrome

Cardiovascular symptoms associated with anaphylactic, anaphylactoid, allergic, or hypersensitivity reactions were first attributed to serum pathology and were characterized as acute carditis, morphologic cardiac reactions, or rheumatic carditis of unknown pathophysiology. The first comprehensive description of allergic angina syndrome as a coronary spasm<sup>20</sup> was described in 1991. This represented a manifestation of endothelial dysfunction or microvascular angina leading to allergic acute myocardial infarction that was later named Kounis syndrome.<sup>21,22</sup> Various inflammatory mediators released during an anaphylactic or allergic reaction or insult, from degranulation of mast cells and other interacting and interrelated cells, including T-lymphocytes, macrophages, eosinophils, and platelets, constitute the main causes of Kounis syndrome. In the Kounis syndrome cascade, histamine, tryptase, and arachidonic acid products, along with chymase acting as a converting enzyme, can promote acute ischemic event coronary spasm, atheromatous plaque erosion/rupture, and platelet activation. Potential inciting causes of Kounis syndrome include drugs, vaccines, hymenoptera stings, metals, foods, environmental exposures, and clinical conditions. This syndrome can affect not only the coronary arteries but also the mesenteric, cerebral, and peripheral arteries, with an incidence ranging from 1.1% to 3.4%

in patients who suffer an allergic, hypersensitivity, anaphylactic, or anaphylactoid insult.<sup>23</sup> Kounis syndrome was first thought to be a rare condition but appears to be an under diagnosed disease.

### Clinical implications and future perspectives

Clinical practice has revealed the following:

1. Adrenaline surge can cause coronary vasoconstriction, reduce coronary blood flow, increase myocardial oxygen demand, worsen myocardial ischemia, and induce both TS and Kounis syndrome.
2. TS has been reported during emotional distress, adrenaline administration, pheochromocytoma-induced adrenergic crisis, anaphylaxis, perioperative anaphylaxis-causing fixation errors,<sup>24</sup> Kounis syndrome, mastocytosis, hymenoptera stings, and even in people witnessing/treating anaphylaxis.
3. Anaphylaxis induces compensatory catecholamine release via the renin-angiotensin-aldosterone system, and the released histamine during anaphylaxis stimulates the further release of catecholamine by direct action on the adrenal medullary cells. Catecholamine increase, with excessive activation of cardiac catecholamine receptors in the left ventricle,<sup>25</sup> plays a major role in the pathophysiology of TS.

4. Kounis syndrome-induced myocardial ischemia or thrombosis by the release of inflammatory mediators during allergic or anaphylactic reactions can be associated with the TS triggered by adrenaline surge.

In conclusion, ATAK constitutes a challenging, contemporary, and novel syndrome. The measurement of some specific anaphylactic inflammatory mediators such as histamine, tryptase, chymase, leukotrienes, thromboxane, and platelet activating factor may help in diagnosing and treating the ATAK complex. Moreover, the use of corticosteroids or mast cell stabilizers for prevention and treatment may elucidate the etiology and pathophysiology of this complex. We urge the research community to “ATTACK ATAK” to clarify its etiology and pathophysiology and apply appropriate preventive and therapeutic measures.

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