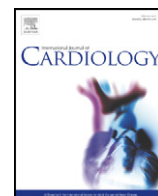




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Editorial

Takotsubo cardiomyopathy, mental stress and the Kounis syndrome

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More than half a century ago, the renowned American physiologist Walter B. Cannon [1] published a paper entitled "Voodoo Death", based on anecdotal experiences, largely from the anthropology literature, of death from fright. He postulated that such a death was caused "by a lasting and intense action of sympathico-adrenal system" [1,2]. Today's phrases "scared to death" [3] and "a broken heart" [4] are deeply rooted in folk wisdom and reflect potentially lethal consequences of emotional, depressogenic or mental stress. In 1971, Engel [5] collected 170 accounts from the lay press of sudden death that were attributed to disruptive life events. He found that such events could be divided into 8 categories: (1) on the impact of the collapse or death of a close person; (2) during acute grief; (3) on threat of loss of a close person; (4) during mourning or on an anniversary; (5) on loss of status or self-esteem; (6) personal anger or threat of injury; (7) after danger is over; and (8) reunion, triumph, or happy ending. Engel proposed that any of these events could provoke neurovegetative responses, involving both the flight-fight and conservation-withdrawal systems, conducive to lethal cardiac events, particularly in individuals with preexisting cardiovascular disease [5].

Stress-induced cardiovascular reactivity has been shown to be associated with carotid intima-media thickness and early atherogenesis [6]. Daily stress is associated with a >2.1-fold increase in risk for developing coronary artery disease and acute myocardial infarction [7], which is similar to the relative risks of diabetes, hypercholesterolemia

and hypertension [8]. Psychosocial stress accounts for 30% of the population attributable risk of acute myocardial infarction [9]. Only smoking and hyperlipidemia account for greater population attributable risk, while hypertension, diabetes and abdominal obesity account for lower population attributable risk [6,8,9].

Takotsubo cardiomyopathy, also referred to as transient left ventricular apical ballooning, stress-induced cardiomyopathy, takotsubo syndrome, apical ballooning syndrome, atypical apical ballooning, ampulla cardiomyopathy, broken heart syndrome, or transient left ventricular dysfunction syndrome [10], was named after a round-bottomed and narrow-necked fishing pot – takotsubo 蛸壺 in Japanese – for trapping octopus, because of its resemblance to the left ventriculogram in these patients. It was first described in 1991 by Dote et al. [11] and popularized 10 years later by Tsuchihashi et al. [12]. It is a clinical condition affecting individuals (mainly postmenopausal women), following emotional distress, resembling acute myocardial infarction, with usually normal coronary arteries on coronary arteriography and transient left ventricular dysfunction. However, there are many questions regarding etiology, pathophysiology and treatment which still remain unanswered.

In the very interesting article of Yoshida et al. [13] published in this journal about a 78-year-old woman with takotsubo cardiomyopathy, the patient developed cardiac rupture, massive hemorrhagic pericardial effusion and left ventricular mural thrombus. Fortunately, the patient survived after surgical performance of a pericardial window and intravenous heparin therapy. Yoshida et al. [13] postulated ventricular rupture associated with coagulation abnormalities and contraction band necrosis. Indeed, on light microscopy, increased eosinophilic staining with preservation of cross-striations and total transformation of the myocardial cytoplasm into dense eosinophilic transverse bands with intervening irregularity have been recognized as the main findings of catecholamine-induced cardiomyopathy since long time ago [14]. Contraction-band necrosis has been described in clinical states of catecholamine excess such as pheochromocytoma [15] and subarachnoid hemorrhage [16]. It has also been observed post mortem in people who died under terrifying circumstances such as fatal asthma [17] and violent assault [18], suggesting that catecholamines may be an important link between emotional stress and cardiac injury. In fact, takotsubo cardiomyopathy has been reported following intravenous administration of epinephrine during an anaphylactic reaction [19] and in association with pheochromocytoma [20].

The precise incidence of patients with takotsubo cardiomyopathy is difficult to ascertain, because its diagnosis has largely been a process of exclusion [21]. The best estimate is 2.1% of female patients and 0.5% of all patients with ST-elevation myocardial infarction, as reported in the

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recently published Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZON-AMI) trial [22]. There certainly has been considerable underdiagnosis [21].

Several reports have associated takotsubo cardiomyopathy with Kounis syndrome [23–26]. Takotsubo cardiomyopathy has been observed not only in patients suffering from anaphylaxis [27] but also in individuals simply observing and assisting in the treatment of anaphylaxis [28]. It has been well established that takotsubo cardiomyopathy represents a stress-induced myocardial stunning [29–31]. Simultaneous multi-vessel coronary artery spasm at epicardial or microvascular levels contributes to the onset of this type of cardiomyopathy [29–31]. There are five pathophysiologic mechanisms for selective ballooning of the left ventricle in takotsubo cardiomyopathy [12,31]:

- (1) The apical segment of the left ventricle does not have a three-layered myocardial structure.
- (2) The apex of the left ventricle is more prone to lose its elasticity after excessive expansion.
- (3) The apex of the left ventricle is the border zone, or locus minoris, of the perfusion of all the major branches of both coronary arteries.
- (4) The apex lags behind in functional recovery from global dysfunction.
- (5) Compensatory transient hypercontraction of the basal segment of the left ventricle produces mid-ventricular obstruction and plays an important role in causing apical ballooning. The latter may contribute to secondary myocardial ischemia due to increased wall tension, causing further ballooning.

Coronary artery spasm by anaphylactic mediators may initiate stress induced cardiomyopathy during anaphylactic reactions [32]. 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 [33]. Catecholamine increase, with excessive activation of cardiac catecholamine receptors in the left ventricle, plays a major role in the pathophysiology of stress-induced cardiomyopathy [34,35]. 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.

Kounis syndrome [36] is defined, today, as the concurrence of acute coronary syndromes with conditions associated with mast cell activation, involving interrelated and interacting inflammatory cells. These inflammatory cells, namely, mast cells, T-cells, and macrophages, activate each other via multidirectional stimuli and behave as a ball of thread. These cells can release inflammatory mediators capable to induce coronary events. Therefore, an important question which arises in cases of Kounis syndrome is whether emotional, depressogenic or mental stress can induce mast cell activation and consequently Kounis syndrome. Experimental findings suggest that cardiac mast cell activation by acute stress may contribute to myocardial ischemia through the release of histamine or proinflammatory mediators [37].

Stress commences with impulses arising from high cortical centers of the brain that are relayed through the limbic system to hypothalamus [38]. 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 coordinator of the stress response which enters the portal venous system of the hypothalamus in order to activate the corticotrophs of the anterior pituitary gland to produce proopiomelanocortin. The latter is cleaved to form adrenocorticotrophic hormone (ACTH). It also stimulates the locus coeruleus, a dense collection of autonomic cells in the brainstem, to secrete norepinephrine at the sympathetic nerve endings. Such an activation of the sympathetic system centrally is also transmitted

to the adrenal medulla to produce large amounts of epinephrine. ACTH stimulates the adrenal cortex to produce corticosteroids. Stress also induces the release of glucagon, growth hormone and homocysteine. The renin-angiotensin system also participates in stress through the sympathetic innervation of the kidney. This entire cascade induces a heightened cardiovascular activity, endothelial injury, myocardial damage, and induction of adhesion molecules on the endothelial cells, to which recruited inflammatory cells adhere and translocate to the arterial wall. An acute phase response, similar to that associated with inflammation, is also engendered, and is characterized by macrophage activation, production of cytokines such as IL-1, IL-6, TNF- α , acute phase proteins, and mast cell activation.

Since anaphylactic reactions can induce stress cardiomyopathy, stress can induce mast cell and other interrelated inflammatory cell activation. Since Kounis syndrome is induced by anaphylactic mechanisms, then the 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. Indeed, research into stress and cardiovascular disease is now at an exciting stage of development and has the potential to deepen our understanding of causal processes and to improve patient care [39].

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [40].

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