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Multiterritorial Reversible Coronary Microvascular Dysfunction as the Main Determinant of Tako-Tsubo Cardiomyopathy

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Tako-tsubo cardiomiopathy (TTC), also known as apical ballooning syndrome or stress cardiomyopapthy, represents an intriguing emerging syndrome with still an uncertain categorization. Although TTC is still classified as cardiomyopathy, its clinical presentation frequently mimics an acute coronary syndrome (ACS), since TTC is usually characterized by acute chest pain associated with ST-segment abnormalities, frequently in anterior leads, and cardiac enzymes release [1]. At coronary angiography TTC patients have absent or mild coronary atherosclerosis and the typical pattern of apical to mid-ventricular a-dyskynesia at ventriculography. Typically myocardial dysfunction completely recovers within days or weeks, thus conferring to TTC a good long-term prognosis.

Some characteristics make TTC an intriguing disease: 1) in the majority of cases TTC is precipitated by an emotional or physical stressful event; 2) TTC usually occurs in female in postmenopausal age; 3) the extent of myocardial dysfunction is disproportionate to the usually mild cardiac enzyme release 4) regional wall motion abnormalities extend beyond a single epicardial vessel distribution [2]. With the aim of understanding the pathophysiology of TTC, these four peculiarities need to be further highlighted.

The frequent finding of a physical or emotional stress precipitating TTC has suggested a possible role of catecholamine release. Wittstein et al. [3] first demonstrated that plasma catecholamine concentration in patients with TTC are two or three times higher than ST-elevation myocardial infarction patients showing hemodynamic compromise (Killip III class) [3]. Consistently with catecholamine-induced myocardial injury, endomyocardial biopsy in these patients reveals mononuclear cell infiltrate and contraction band necrosis. These findings have been further confirmed in later studies showing an improved cardiac sympathethic activity in the apical myocardium. The reason why the apex is frequently affected and the base always spared probably resides in a greater density of β-adrenergic receptor in these region, thus conferring to cardiac apex a higher vulnerability to sudden catecholamine release. High levels of circulating catecholamine might determine micro vascular spasm, damage and hypo contraction of the myocardial muscle, mostly due to disturbance of the intracellular calcium regulatory system [4]. Although catecholamine-induced myocardial damage can be appropriately considered a very common finding in TTC, it has to be noticed that TTC does not always follow a stressful event and that a raise in catecholamine plasma levels can be detected in only 70% of patients affected by TTC.

The clinical occurrence of TTC in post menopausal women supports a pathogenic role of estrogens reduction. Indeed, estrogens play an important regulatory role on the release of epinephrine in the pre-synaptic cardiac sympathetic nerves [5]. This mechanism seems to be essential to protect myocardium from adrenergic stress occurring during pregnancy and delivery. Moreover, estrogens are involved in the regulation of intracellular calcium metabolism, thus affecting endothelial and myocardial cells contraction. For these reasons, it can be speculated that estrogens depletion might be considered a condition favouring catecholamine-mediated damage in TTC [6].

With regard to cardiac enzyme release in TTC, it has to be observed that cardiac troponin usually peaks within 24 hours after clinical onset and that the amount of myocardial necrosis is much lower than that observed in the setting of acute myocardial infarction. Indeed, the limited extension of myocardial necrosis with respect to the large reversible myocardial dysfunction is a peculiarity of TTC.

Another characteristic of TTC is the "multi territoriality" of myocardial dysfunction that is its extension beyond a single vessel territory. Several studies have proposed multi vessel coronary spasm [7] as main pathophysiologic mechanism in TTC. However, the spontaneous or pharmacologically-induced coronary epicardial spasm was found in no more that 30% of Japanese patients. Moreover, these data have not been confirmed in Western patients. This considered, the characteristic of multi territoriality in TTC allow to rule out the direct involvement of epicardial coronary vessels, either by a functional spasm or a spontaneous thrombus lysis, among the possible etiologies of the syndrome.

If multiple etiopathogenetic mechanisms can cause TTC, is there a common pathophysiologic mechanism? Several studies have pointed out the possible role of coronary micro vascular constriction as the main determinant of left ventricular wall motion abnormalities commonly found in this syndrome. In a small cohort of TTC patients, Bybee et al. [8] first observed a reduced TIMI (Thrombolysis in Myocardial Infarction) frame counts, thus suggesting a condition of coronary microvascur dysfunction [8]. Notably, TIMI frame count was reduced in all patients and diffused to all three coronary vessels. These findings are consistent with those published by by Meimoun et al. [9] and Rigo et al. [10] showing a reduction of coronary flow reserve, as assessed by transtoracic Doppler, in multiple coronary vessels and its spontaneous improvement of at 3-week follow up. Our group has recently expanded these observations. Using myocardial contrast echocardiography, we found a transmural myocardial perfusion defect within dysfunctional myocardium in TTC few days after the onset of symptoms [11]. This perfusion defect was partially or totally reversible during adenosine infusion, promptly returning to basal condition at the end of vasodilator challenge. Finally, the pattern of hypo perfusion totally resolved after 1 month together with the recovery of myocardial contractility. The

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transient improvement of micro vascular perfusion during adenosine challenge and the complete recovery of both perfusion and contractility at follow-up, a phenomenon that was present in all our studied TTC patients, strongly indicate the functional nature of coronary micro vascular dysfunction representing a common pathophysiological mechanism in TTC.

Even after 20 years of its initial description by Dote [7], TTC is still a mysterious disease. Several evidences, however, suggest that TTC is sustained by a common pathophysiological mechanism represented by coronary micro vascular vasoconstriction. The condition of coronary micro vascular dysfunction is consistent with the myocardial stunning that characterizes the disease, as evident by the transient nature of contractile dysfunction and the mild cardiac enzyme release, and with the multi territorial distribution of contractile dysfunction. The condition of CMD is also consistent with the hypothesis of catecholamine toxicity, which may directly induce micro vascular spasm. In addition, endothelial dysfunction or a higher susceptibility to catecholamine-induced micro vascular vasoconstriction due to estrogen depletion may play a determinant role. If the pathophysiological mechanism is clarified, on the other hand the search for TTC etiology has to go on. With this regard, in order to expand therapeutically options and improve prognosis by preventing TTC relapses, clinicians must be encouraged to try to identify the correct etiology each time they have to face a TTC patient.

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