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**Is Takotsubo cardiomyopathy still looking for its own nosological identity?**

Riccardo Scagliola, Gian Marco Rosa

**Abstract**

Despite several efforts in providing a proper nosological framework for Takotsubo cardiomyopathy (TCM), this concern remains an unresolved matter in clinical practice. Several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of myocardial infarction with non-obstructive coronary arteries. Further investigations are needed in order to define TCM with the most appropriate disease taxonomy.

**TO THE EDITOR**

Despite several efforts in providing a proper nosological framework for Takotsubo cardiomyopathy (TCM), this concern remains an unresolved matter in clinical practice. Current revised Mayo Clinic diagnostic criteria for TCM include i) the presence of transient left ventricular wall motion abnormalities (either hypokinesis, akinesis or dyskinesis) with or without apical involvement, ii) usually extending beyond a single epicardial vascular distribution, iii) in the absence of obstructive coronary artery disease on coronary angiography, iv) associated with new electrocardiographic abnormalities or modest troponin increment, v) in the absence of pheochromocytoma or myocarditis[1]. Subsequently, the International Takotsubo Diagnostic Criteria (interTAK Diagnostic Criteria) provided following additional criteria in order to improve the identification of TCM: a) cases with wall motion abnormalities related to the
distribution of a single epicardial coronary artery should not be considered an exclusion criteria of TCM; b) pheochromocytoma, as well as neurologic disorders (i.e. subarachnoid haemorrhage, ischaemic stroke or transient ischaemic attack) are recognized as secondary causes of TCM, and c) the presence of coronary artery disease does not represent and exclusion criteria of TCM[2]. This latter additional finding and the contextual detection of obstructive epicardial coronary lesions make the distinction between acute coronary syndrome and TCM more challenging in clinical practice[3]. In this regard, whether TCM should be classified as a distinct subset of myocardial infarction with non-obstructive coronary arteries (MINOCA) is still controversial. In a comprehensive review by Vidal-Perez et al, TCM was included within the wide nosological spectrum of MINOCA[3]. However, emerging clinical and pathophysio logic findings in the literature have progressively raised doubts concerning this current taxonomy. In a retrospective analysis conducted by Lopez-Pais et al on a large multicenter registry, patients with TCM showed a different clinical profile compared to those belonging to the other subsets of MINOCA. Specifically, TCM was more frequently detected as an intercurrent complication during hospitalization for other causes, and was characterized by a much more aggressive acute phase and by a better long-term prognostic outcome, compared to patients affected by the other forms of MINOCA[4]. Additionally, when present, some electrocardiographic findings can also help in distinguishing between TCM and the other subsets of MINOCA. In particular, the absence of Q waves or reciprocal changes of ventricular repolarization, a ratio between ST-segment elevation in leads V4-V6 and V1-V3 > 1 and the presence of ST-segment depression in lead aVR in the absence of ST-segment elevation in lead V1 have been reported to detect TCM with a high predictive accuracy[5,6]. Furthermore, different pathophysiological processes have been shown to be involved in developing reversible wall motion abnormalities which characterize TCM, compared to the rest of MINOCA subsets (Table 1). Although microvascular dysfunction has been hypothesized to be involved in pathogenetic mechanisms of TCM, it seems to represent a mere epiphenomenon compared to the catecholaminergic surge related to sympathetic
hyperactivity, which is mediated by both central and autonomic nervous system in response to psychophysical or environmental stressors. Specifically, a direct catecholamine toxicity and the effects of norepinephrine spillover from the cardiac sympathetic nerve terminals, have been shown to be the greatest responsible mechanisms of wall motion abnormalities detected in TCM, as demonstrated by the congruent distribution of cardiac nervous terminals to the affected segments of myocardial wall. This is reflected in a typical histopathological pattern called myocytolysis, which is characterized by areas of early myofibrillar damage, hypercontracted sarcomeres and a mononuclear inflammatory response. These histological features are distinct from those noticed in the rest of patients with MINOCA (which are instead characterized by atonic myocytes, with no myofibrillar damage and polymorphonuclear infiltrates), and are not primarily induced by vasoconstriction, but by a direct effect of catecholamines on cardiac β-adrenergic receptors (like other conditions related to catecholamine surge, as in the case of pheochromocytoma or subarachnoid hemorrhage). As reported by Santoro and coworkers, histologic findings confirm how TCM and acute coronary syndromes are sustained by two different inflammatory patterns. In particular, high levels of anti-inflammatory interleukins detected in TCM (particularly IFN-α and IFN-γ) have been shown to be related to the presence of M2 macrophages surrounding the impaired myocardial tissue, and to their capability in removing damaged cells and preserving healthy tissue, thus favoring a complete functional recovery in this subset population. Finally, the presence of transient and reversible transmural myocardial edema involving the dysfunctional wall segments on T2-weightened imaging, in the absence of late gadolinium enhancement, represents a pathognomonic hallmark provided by cardiac magnetic resonance in TCM patients, compared to the rest of MINOCA subjects. In conclusion, several clinical, pathophysiologic and histologic findings support the conceivable hypothesis that TCM could be defined as a unique pathologic entity, rather than a distinct subset of MINOCA. These issues need to be
confirmed by further investigations, in order to define TCM with the most appropriate
disease taxonomy.

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