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Editorial Board Member of *World Journal of Cardiology*, Akshyaya Pradhan, MD, DM, FACC, FSCAI, FESC, FAPSIC, Professor (Jr), Department of Cardiology, King George's Medical University, Lucknow, Uttar Pradesh 226003, India. akshyaya33@gmail.com

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

Riccardo Scagliola, Gian Marco Rosa

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**Riccardo Scagliola, Gian Marco Rosa**, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Genoa 16132, Italy

**Corresponding author:** Riccardo Scagliola, MD, Doctor, Cardiovascular Disease Unit, IRCCS Ospedale Policlinico San Martino, Largo R. Benzi n. 10, Genoa 16132, Italy. [risca88@live.it](mailto:risca88@live.it)

### Abstract

Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this 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.

**Key Words:** Takotsubo cardiomyopathy; Myocardial infarction with non-obstructive coronary arteries; Disease classification

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**Core Tip:** Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this 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. These issues need to be confirmed by further investigations, in order to define TCM with the most appropriate disease taxonomy.

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## TO THE EDITOR

Despite several efforts to provide a proper nosological framework for Takotsubo cardiomyopathy (TCM), this remains an unresolved matter in clinical practice. Current revised Mayo Clinic diagnostic criteria for TCM include: (1) The presence of transient left ventricular wall motion abnormalities (either hypokinesis, akinesis or dyskinesis) with or without apical involvement; (2) usually extending beyond a single epicardial vascular distribution; (3) in the absence of obstructive coronary artery disease on coronary angiography; (4) associated with new electrocardiographic abnormalities or modest troponin increment; and (5) in the absence of pheochromocytoma or myocarditis[1]. Subsequently, the International Takotsubo Diagnostic Criteria (interTAK Diagnostic Criteria) provided the following additional criteria in order to improve the identification of TCM: (1) Cases with wall motion abnormalities related to the distribution of a single epicardial coronary artery should not be considered an exclusion criteria of TCM; (2) pheochromocytoma, as well as neurologic disorders (*i.e.* subarachnoid hemorrhage, ischemic stroke or transient ischemic attack) are recognized as secondary causes of TCM, and (3) the presence of coronary artery disease does not represent an exclusion criterion 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*[3], TCM was included within the wide nosological spectrum of MINOCA. However, emerging clinical and pathophysiologic findings in the literature have progressively raised doubts concerning this current taxonomy. In a retrospective analysis conducted by Lopez-Pais *et al*[4] 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. Additionally, when present, some electrocardiographic findings can also help to distinguish 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  $V_4$ - $V_6$  and  $V_1$ - $V_3$   $> 1$  and the presence of ST-segment depression in lead aVR in the absence of ST-segment elevation in lead  $V_1$  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 the pathogenic mechanisms of TCM, it seems to represent a mere epiphenomenon compared to the catecholaminergic surge related to sympathetic hyperactivity, which is mediated by both the central and autonomic nervous system in response to psychophysical or environmental stressors[7]. Specifically, 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 the myocardial wall[8]. 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 noted in the rest of patients with MINOCA (which were instead characterized by atonic myocytes, with no myofibrillar damage and polymorphonuclear infiltrates), and were not primarily induced by vasoconstriction, but by a direct effect of catecholamines on cardiac  $\beta$ -adrenergic receptors (like other conditions related to the catecholamine surge, as in the case of pheochromocytoma or subarachnoid hemorrhage)[9,10]. 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- $\alpha$  and IFN- $\gamma$ ) 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[11]. Finally, the presence of transient and reversible transmural myocardial edema involving the dysfunctional wall segments on T2-weighted 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[12]. 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.

**Table 1** Characterizing the differences between Takotsubo cardiomyopathy and myocardial infarction with non-obstructive coronary arteries

	Takotsubo cardiomyopathy	MINOCA
Clinical findings	A more aggressive acute phase despite a better long-term cardiovascular prognosis	A less aggressive acute phase despite a worse long-term cardiovascular prognosis
Main pathophysiologic mechanisms	Sympathetic hyperactivity and a direct effect of catecholamines on $\beta$ -adrenergic receptors of cardiomyocytes	Coronary plaque disruption; Coronary vasospasm; Spontaneous coronary artery dissection; Microvascular dysfunction; Coronary thromboembolism
Histopathologic lesions	Areas of myofibrillar damage with hypercontracted sarcomeres and mononuclear infiltrates	Absence of myofibrillar damage with atonic sarcomeres and polymorphonuclear infiltrates
Location of myocardial lesions	Around intracardiac nervous terminals	Around cardiac vessels
Inflammatory patterns	Increased levels of anti-inflammatory interleukins, able to remove damaged cells and preserve healthy myocardial tissue	Increased levels of pro-inflammatory interleukins, able to promote coronary plaque disruption and microvascular impairment
CMR findings	Transient and reversible transmural myocardial edema on T2-weighted imaging in the absence of late gadolinium enhancement	Late gadolinium enhancement (either subendocardial or transmural) with or without myocardial edema on T2-weighted imaging

CMR: Cardiac magnetic resonance; MINOCA: Myocardial infarction with non-obstructive coronary arteries.

## FOOTNOTES

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**Country/Territory of origin:** Italy

**ORCID number:** Riccardo Scagliola 0000-0002-5439-3300; Gian Marco Rosa 0000-0003-0809-2301.

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