

REVIEW ARTICLE—DISEASE DISCOVERED IN JAPAN AND THE ROLE OF NUCLEAR CARDIOLOGY

Takotsubo Syndrome: Changes in Diagnostic Criteria and Role of Nuclear Imaging

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Abstract

Takotsubo syndrome (TTS) was first described in 1990. A wide variety of TTS cases have been reported since then; the international consensus has proposed several diagnostic criteria. The current diagnostic system often relies on identifying combinations of subsets of symptoms, or criteria, to define diagnoses. In the recently proposed TTS diagnostic criteria, obstructive coronary syndrome and pheochromocytoma involvement changes. Here, we review the criteria and the role of nuclear imaging in TTS diagnosis and discuss new directions that can provide better information

Keywords: Acute coronary syndrome, Diagnosis, Nuclear imaging, Takotsubo syndrome

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Takotsubo syndrome (TTS) is characterized by transient regional systolic dysfunction in the left ventricle. The dysfunctional area is not corresponding to the coronary artery perfusion territory and often including the circumferential apical, mid-ventricular, and/or basal ventricle. TTS is relatively novel; the first TTS case was reported in 1990 by Sato, et al. in Japan (1). Since then, Many TTS cases have been reported worldwide under the multiple names, such as stress cardiomyopathy, apical ballooning syndrome, broken heart syndrome and catecholamine induced cardiomyopathy. The various data of TTS have been accumulated, although, its diagnosis remains controversial.

The clinical presentation of TTS in electrocardiographic changes and abnormal serum biomarkers is similar to that of acute coronary syndrome (ACS). The pathophysiology of TTS remains unclear. The latest hypothesis consider it as the integrated cardiovascular response to sudden surges in endogenous catecholamine concentrations or to exogenously administered catecholamines often in the context of acute severe stress (2). Accordingly, the diagnosis of TTS is still challenging because of ACS like clinical phenotype and unclear pathogenesis. The prognosis of TTS was initially reported to be favorable compared with that of ST-segment

elevated myocardial infarction, whereas subsequent studies have demonstrated that the acute and long-term mortality in TTS are higher than previously recognized (3, 4). Therefore, the accurate diagnosis is crucial for this entity. Here, we review the diagnostic criteria of TTS and discuss the availability of nuclear imaging in its diagnosis.

Changes in diagnostic criteria

The first diagnostic criteria were introduced by Abe et al. in 2003. Several criteria have been published since then; the Mayo Clinic Diagnostic Criteria are the most commonly applied (5). The conventional criteria have proposed the exclusion of significant stenosis of the coronary artery; however, the recent data have demonstrated that coronary artery disease (CAD) is frequently observed in patients with TTS (3). When the patients have CAD, the diagnosis of TTS become notably complicated. Such patients are more likely to be misdiagnosed as having ACS. The presence of obstructive CAD should not be considered as an exclusion criterion (6).

Pheochromocytoma is a rare neuroendocrine tumor derived from the medulla of the adrenal gland or extra-adrenal chromaffin tissue, and it secretes enormous catecholamines. Catecholamine storm triggers electrocardiographic abnormali-

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Table 1 Changes in diagnostic criteria for takotsubo syndrome

Mayo Clinic (2008) (5)	<ol style="list-style-type: none"> 1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present. Electrocardiographic changes in ST-segment elevation or T wave inversion. 2. The Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. 3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin. 4. The Absence of Pheochromocytoma and myocarditis.
Position Statement from the HFA of the European Society of Cardiology (2016) (7)	<ol style="list-style-type: none"> 1. Transient regional wall motion abnormalities of left ventricular or right ventricular myocardium that precede frequently, but not always, by a stressful trigger (emotional or physical). 2. The regional wall motion abnormalities usually* extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved. 3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis). 4. New and reversible electrocardiographic (ECG) abnormalities (ST-segment elevation, ST depression, LBBB †, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months). 5. Significantly elevated serum natriuretic peptide (BNP or NT-proBNP) during the acute phase 6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (i.e. disparity between the troponin level and the amount of dysfunctional myocardium present). 7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3-6 months).
International Expert Consensus (2018) (6)	<ol style="list-style-type: none"> 1. Patients show transient left ventricular dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular-, basal-, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall-motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where a coronary lesion is present in the subtended myocardial territory of the wall-motion abnormality. Therefore, coronary artery disease is not a contradiction in takotsubo syndrome. 2. An emotional, physical, or combined trigger can precede the takotsubo syndrome event, but this is not obligatory. 3. The presence of neurologic disorders (e.g. subarachnoid hemorrhage, stroke/transient ischemic attack, seizures) as well and pheochromocytoma do not exclude the diagnosis of takotsubo syndrome. 4. New ECG abnormalities, including ST-segment elevation, ST-segment depression, T-wave inversion and QTc prolongation are present; however, rare cases exist without any ECG changes. 5. The levels of cardiac biomarkers, such as troponin and creatine kinase, are moderately elevated in most cases; significantly elevated BNP is common. 6. Patients have no evidence of infectious myocarditis. 7. Postmenopausal women are predominantly affected.

ties, left ventricular systolic dysfunction, and an increase in the biomarkers; thus, it should be considered as the main pathophysiology of TTS. The conventional diagnostic criteria have excluded pheochromocytoma as a specific cause of TTS, whereas the clinical phenotype of TTS is consistent with that of pheochromocytoma. The diagnostic criterion of European Society of Cardiology thus includes pheochromocytoma as a secondary cause of TTS (7).

Based on the above-mentioned situation and current knowledge, the international expert consensus has provided new diagnostic criterion of TTS, International Expert Consensus Document on TTS, which helps to improve identification and classification of TTS (6). In the new criterion, it is noteworthy that coronary artery disease is not a contradiction in TTS and pheochromocytoma do not exclude

the diagnosis of TTS (Table 1).

The role of nuclear cardiology

The nuclear imaging assesses coronary perfusion; cardiac metabolic function and sympathetic nervous are closely associated with the onset of TTS. The role of nuclear imaging in TTS diagnosis has not been well established yet. So far, no diagnostic criteria describe the usefulness of nuclear imaging in TTS diagnosis, which is already discussed in some papers (7, 8). Nuclear imaging provides useful information, particularly on CAD and pheochromocytoma combined with TTS.

TTS should be distinguished from ACS; then, nuclear metabolic imaging greatly contribute to the accurate diagnosis. One study concluded that fatty-acid metabolism depicted by ¹²³I-BMIPP myocardial scintigraphy was more severely

impaired than myocardial perfusion depicted by ^{201}Tl scintigraphy in acute phase of TTS patients (9). The discrepancy between $^{99\text{m}}\text{Tc}$ scintigraphy and ^{123}I -BMIPP scintigraphy is markedly lower in TTS than ST-segment elevated myocardial infarction (10). Under the perfusion tracers, the reduction of apical counts occurs by regional myocardial wall thinning in the apex, which is due to not the artifact but the partial volume effects. Others, it might be due to reduced regional perfusion in the takotsubo infarcted area and increased perfusion in non-takotsubo area or combined all these factors. No study has presented the use of stress-rest gated single-photon emission computed tomography in patients with TTS; it provides the evaluation of not only perfusion but also global and regional functions as well as the possible presence of ischemia.

^{123}I -MIBG scintigraphy assesses myocardial sympathetic nerve terminal activity and detects adrenal and ectopic pheochromocytoma. Even in the subacute phase of TTS, decreased delayed H/M ratio and increased washout rate of ^{123}I -MIBG represent the adrenergic hyperactivity in patients with TTS (11). The uptake of ^{123}I -MIBG is impaired for months, and it is corresponding to a regional disturbance of sympathetic neuronal activity (12). The combination of ^{123}I -MIBG scintigraphy and myocardial perfusion scintigraphy is useful to distinguish TTS from ACS in which innervation and myocardial scarring is matched.

Cardiac positron emission tomography (PET) using [^{18}F]2-fluoro-deoxy-glucose (FDG) depicts abnormal glucose metabolism in normal myocardial perfusion in patients with TTS; one of the recent studies demonstrated heterogeneous accumulation of FDG in the patients with TTS (13). One study using $^{13}\text{NH}_3$ / ^{82}Rb PET demonstrated impaired left ventricular perfusion in the acute phase and unchanged midventricular and apical flow in the acute and follow-up phases (14). Global left ventricular hyperemia and impaired coronary flow reserve (CFR) in the takotsubo infarcted area have been presented in their case series (14). In typical TTS, basal hyperperfusion probably caused by regionally increased metabolic requirement in which basal contractility increases to compensate for failing the heart. Also, it should be kept in mind that the findings of perfusion and CFR depend on the timing of acquiring the images after the onset of TTS.

Conclusion

The diagnostic criteria of TTS is updated; CAD and pheochromocytoma are also included into the new criteria. Therefore, it seems that now is favorable time to assess the availability of nuclear imaging for providing more accurate TTS diagnosis.

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Conflicts of interest

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