EDITORIAL

Modification of Diagnostic Criteria in Takotsubo Syndrome

Modificación de los criterios diagnósticos en el síndrome de Takotsubo

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Takotsubo syndrome (TTS) is characterized by transient regional systolic dysfunction in the left ventricle. The dysfunctional areas do not correspond to the coronary artery perfusion territory and are often identified in the circumferential apical, mid-ventricular, or basal ventricle. This syndrome is a relatively novel concept: the first report of TTS was described in 1990 by Sato, et al. in Japan. (1) Following this first case, numerous TTS cases have been globally reported under multiple names, such as stress cardiomyopathy, apical ballooning syndrome, broken heart syndrome and catecholamine induced cardiomyopathy. Since then, although various data obtained from TTS cases have been accumulated, controversies remain about the diagnostic criteria. Arias et al. have reported the clinical features of TTS in their hospital located in Buenos Aires, Argentina. (2) Their report plays an important role in the field of TTS, since most of the registered data is originated from countries in the northern hemisphere.

Arias, et al. described that the clinical features of TTS were similar to those of acute coronary syndrome (ACS), including ECG changes and abnormal serum biomarkers. They also reported that female predominance in TTS was the same as in the study by Lyon, et al., (2, 3) and demonstrated that NT-proBNP concentration was the prognostic indicator in patients with TTS. The current classification for TTS severity suggests that elevated BNP concentration is associated with higher risk and such patients should be treated in the intensive care unit. Arias et al., described in their study a cut-off value of NT-proBNP >12000 ng/L, (2) whereas this was >2000 ng/L in the report of Lyon, et al. (3) This author defined high-risk patients as follows:

1. Patients >75 years
2. Systolic blood pressure <110 mmHg
3. Presence of lung edema
4. Patients with complicated with or lethal arrhytmias
5. Patients with severe systolic dysfunction (left ven tricular ejection fraction <35%)
6. Outflow tract pressure gradient >40 mmHg
7. Presence of mitral regurgitation
8. Patients with cardiac thrombus
9. Patients complicated with ventricular septal perforation
10. Patients with left ventricle ventricular rupture
11. Patients with prolonged QT interval
12. Presence of abnormal Q wave
13. Patients with fluctuating ST-segment elevation
14. BNP ≥600 or NT-proBNP ≥2000 ng/L
15. Right ventricular involvement.(3)

When a patient with TTS is classified as having high risk, it is necessary to observe his/her hemodynamics for more than 72 hours in the intensive care unit. Moreover, the patient with significant symptoms should have delayed enhancement cardiac magnetic resonance (CMR) imaging, since an earlier conducted study demonstrated that in approximately 10% of the study patients who received CMR imaging at the time of initial clinical presentation, it provided relevant functional and tissue information that could aid in the establishment of TTS diagnosis. (4) Various other left ventricular wall motion abnormalities in TTS patients have been reported. A study found that nearly 20% of all TTS patients did not have typical apical ballooning of the left ventricle but variants of left ventricular dysfunction. (5) However, in the present study, no alternative forms were presented; hence, the TTS variants were possibly misdiagnosed. We should closely look for various patterns of ventricular contraction in the acute phase of TTS.

The present study demonstrated that patients with TTS who had coronary artery stenosis did not present high in-hospital mortality. In general, TTS is not associated with acute plaque rupture in the coronary arteries. Some studies reviewing cohorts of TTS patients have reported that bystander coronary artery disease accounts for 10% of TTS cases. (6, 7) The pathophysiology of TTS remains unclear. The latest hypotheses have considered it as the integrated cardiovascular response to a sudden surge in endogenous catecholamine concentrations or to exogenously administered catecholamines in acute severe stress. (8) Because of the acute coronary syndrome-like clinical features and the unclear pathophysiology, the diagnosis of TTS is still challenging. The prognosis of TTS

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Table 1. Changes of Diagnostic Criteria for Takotsubo Syndrome

Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology (2015) (3)	1. Transient regional wall motion abnormalities of the left or right ventricular myocardium which are frequently, but not always, preceded 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. 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 left ventricular dysfunction observed (e.g. hypertrophic cardiomyopathy, viral myocarditis).** 4. New and reversible electrocardiographic abnormalities (ST-segment elevation, ST-segment depression, left bundle branch block†, 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 of 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 studies at follow-up (3-6 months).
International Expert Consensus (2018 accepted) (11)	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. In addition to 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 as **pheochromocytoma does not exclude the diagnosis of takotsubo syndrome**. 4. Presence of new electrocardiographic abnormalities (ST-segment elevation, ST-segment depression, T-wave inversion, QTc prolongation); however, rare cases exist without any ECG changes. 5. Cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common. 6. Patients have no evidence of infective myocarditis. 7. Postmenopausal women are predominantly affected.

was initially reported favorable compared with that of ST-segment elevated myocardial infarction, whereas subsequent studies have demonstrated that acute and long-term mortalities are higher than previously recognized. (5, 9) Therefore, an accurate diagnosis is crucial for the patients with TTS.

Regarding diagnosis, the first TTS criteria introduced by the Mayo Clinic were the most commonly employed. (10) The conventional criteria proposed the exclusion of significant coronary artery stenosis; however, recent criteria accepted the presence of coronary artery disease in patients with TTS. Since the presence of obstructive coronary artery disease should not be included in the exclusion criteria, these should be revised. Although conventional diagnostic criteria have excluded pheochromocytoma as a specific cause of TTS, the clinical features of TTS coincide with those of this tumor. The European Society of Cardiology is going to present the novel diagnostic criteria, including pheochromocytoma and subarachnoid hemorrhage as secondary causes of TTS. (11)

CONFLICTS OF INTEREST

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

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