STATE-OF-THE-ART REVIEW ARTICLE

Standard and Advanced Echocardiography in Takotsubo (Stress) Cardiomyopathy: Clinical and Prognostic Implications

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Echocardiography is frequently the initial noninvasive imaging modality used to assess patients with takotsubo cardiomyopathy (TTC). Standard transthoracic echocardiography can provide, even in the acute care setting, useful information about left ventricular (LV) morphology as well as regional and global systolic or diastolic function. It allows the differentiation of different LV morphologic patterns according to the localization of wall motion abnormalities. A "circumferential pattern" of LV myocardial dysfunction characterized by symmetric wall motion abnormalities involving the midventricular segments of the anterior, inferior, and lateral walls should be considered suggestive of TTC and included in the differential diagnosis of acute coronary syndromes. Moreover, advanced echocardiographic techniques, including speckle-tracking, myocardial contrast, and coronary flow studies, are providing mechanistic and pathophysiologic insights into this unique syndrome. Early identification of any potential complications (i.e., LV outflow tract obstruction, reversible moderate to severe mitral regurgitation, right ventricular involvement, thrombus formation, and cardiac rupture) are crucial for the management, risk stratification, and follow-up of patients with TTC. Because of the dynamic evolution of the syndrome, comprehensive serial echocardiographic examinations should be systematically performed. This review focuses on these aspects of imaging and the increasing understanding of the clinical and prognostic utility of echocardiography in TTC. (J Am Soc Echocardiogr 2015;28:57-74.)

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Takotsubo cardiomyopathy (TTC), also known as stress cardiomyopathy, left ventricular (LV) apical ballooning syndrome, or broken heart syndrome, is a unique cardiac syndrome characterized by transient LV systolic dysfunction often mimicking an acute myocardial infarction (AMI). It is usually precipitated by acute emotional and/or physical stress and is characterized by three distinctive features: (1) the presence of acute LV wall dysfunction, (2) the absence of significant obstructive coronary artery disease and (3) the rapid improvement of LV systolic function within a few days or weeks.[1,2]

The development of TTC most likely reflects the cardiac response to a surge of catecholamines, often triggered by a stressful event. In fact, serum epinephrine levels have been shown to be significantly higher in patients with TTC than in patients with acute ischemic heart failure, suggesting an excessive hypothalamic-pituitary-adrenal axis response to stress.[3] Of note, also the infusion of epinephrine or dobutamine for therapeutic or diagnostic purposes has been reported to precipitate TTC.[4] A number of additional mechanisms have been proposed to explain the classical apical dysfunction observed in TTC. These include multivessel coronary vasospasm, aborted myocardial infarction with plaque rupture, thrombus formation and dissipation, vasospasm of a large "wrap-around" left anterior descending coronary artery (LAD) anatomy, or direct catecholaminergic effects on the myocardium.[5] However, the exact pathophysiology of TTC remains to be clearly defined.

All available studies report a marked female predominance in TTC, affecting postmenopausal women in 90% of cases, with an age range of 60 to 75 years.[6] Men are in a similar age range and account for about 10% of the patient population. Overall, <10% of TTC patients are below 50 years of age. The exact incidence of TTC is unknown, at least in part as a result of widespread underdiagnosis.[7] Among patients undergoing coronary angiography for suspected acute coronary syndrome, about 2% are diagnosed as having TTC[8] (Figure 1).

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Abbreviations

AMI = Acute myocardial infarction

CFR = Coronary flow reserve

CMR = Cardiac magnetic resonance

EF = Ejection fraction

LAD = Left anterior descending coronary artery

LV = Left ventricular

LVOTO = Left ventricular outflow tract obstruction

MCE = Myocardial contrast echocardiography

MR = Mitral regurgitation

RT3DE = Real-time three-dimensional echocardiography

RV = Right ventricular

SAM = Systolic anterior motion of the mitral valve

TIN = Tako-Tsubo Italian Network

TTC = Takotsubo cardiomyopathy

TTE = Transthoracic echocardiography

WMA = Wall motion abnormality

Patients with TTC have generally a good short-term prognosis, with a rapid improvement of LV systolic function within a few days or weeks.[9,10] A variety of complications may occur in the acute phase of the disease, such as acute heart failure with pulmonary edema or cardiogenic shock, intraventricular pressure gradients, acute functional mitral regurgitation (MR), right ventricular (RV) dysfunction, intraventricular thrombi resulting in stroke or arterial embolism, atrial fibrillation, or malignant ventricular arrhythmias.[11] Rarely, perforation of the LV free wall or the interventricular septum has been described. In large studies, in-hospital mortality was observed in about 2% of patients with TTC.[9,10] On the other hand, newer studies suggest that both short- and long-term mortality may be substantial and similar to that of patients with acute coronary syndromes.[12]

Notwithstanding this, patients with TTC show more favorable outcomes than those with AMIs with a similar degree of LV dysfunction at presentation.[8] The reported frequency of TTC recurrence ranges from 0% to 11.4%.[13]

Prompt imaging of ventricular function is the key to mak-ing the diagnosis. Because of its widespread availability and feasibility in the acute care setting, echocardiography is frequently the first noninvasive imaging modality used to assess patients with TTC. It can provide useful information on LV morphology and regional and global systolic or diastolic function. In addition, features that have been associated with TTC, such as LV outflow tract obstruction (LVOTO), MR, and RV involvement, can also be detected. Echocardiography also allows the noninvasive assessment of coronary microcirculation impairment during the acute phase of TTC. In this review, we discuss each of these topics, with a special focus on clinical and prognostic implications.

STANDARD ECHOCARDIOGRAPHIC ASSESSMENT

LV Systolic Function

In the acute phase, transthoracic echocardiography (TTE) usually identifies the characteristic LV morphology associated with TTC. Standard TTE allows the detection of the different LV morphologic patterns according to the localization of wall motion abnormalities (WMAs).[14-16] In the majority of cases, WMA typically involve the apical and midventricular segments, which appear akinetic or dyskinetic (defined as "apical ballooning") in contrast to the basal segments, which are often hyperkinetic. Several variant forms, such as "midventricular" or "inverted" TTC, have also been described. Midventricular TTC is characterized by akinesis of the midventricular segments, mild hypokinesis, or normal contraction of the apical segments and hypercontractility of the base. Inverted TTC is characterized by two different forms, the first defined as "apical sparing" with preserved apical function and severe hypokinesis of the remaining walls, and the second as "basal or reverse' TTC with hypokinesis confined to the basal segments. The prevalence of these variant forms remains uncertain. In a large cohort of patients with TTC enrolled in the Tako-Tsubo Italian Network (TIN), midventricular and inverted TTC variants were detected in 18.1% and 4.8% of cases, respectively.[17]

Kurowski *et al.*[18] found no differences in demographic, clinical, angiographic, and laboratory parameters or outcomes in patients with typical apical TTC compared with those with midventricular TTC. Mansencal *et al.*[19] reported that patients without apical involvement were younger, with less impaired systolic function and fewer signs of heart failure. Nevertheless, there were no differences among the several forms of TTC in LV function recovery at early and late follow-up.

In the acute phase, LV ejection fraction (EF) is reduced in patients with TTC and recovers with resolution of myocardial stunning.[1,2] The degree of EF reduction varies according to the severity of myocardial impairment, the presence of comorbidities, and age.[6,9] The magnitude of myocardial dysfunction is wide and irrespective of single coronary artery territory distribution, while the degree of biomarker release is quite small in proportion to the extent of WMAs. In fact, there is a discrepancy between the mild elevations in troponin levels and the extent of myocardial dysfunction. This contrasts with the situation in acute ST-segment elevation myocardial infarction, in which the peak troponin value is usually high in relation to the extent of regional dysfunction. On this ground, the product of peak troponin I level and echocardiographically derived LV EF ($\geq$250) has recently been used as an index to differentiate TTC from ST-segment elevation myocardial infarction, with sensitivity and specificity of 95% and 87%, respectively.[20] In a previous study, Dib *et al.*[21] compared patients with TTC according to different electrocardiographic patterns at presentation and found no differences in clinical characteristics, EF, and outcomes.

In a systematic review of 28 case series, Pilgrim and Wyss[22] reported a marked depression of LV EF on admission, followed by substantial improvement after 18 days on average (mean time range to recovery, 7–37 days; EF 20%–49.4% vs 59%–76% after recovery) in patients affected by TTC, suggesting the usefulness of this index in monitoring LV systolic function recovery. A marked reduction in LV EF on admission with improvement at short-term follow-up was also reported in the TIN registry (mean EF, 37.5 $\pm$ 5.2% vs 55.5 $\pm$ 7.1% at short-term follow-up[17]; Table 1). Furthermore, LV EF seems to be an independent predictor of major complications, providing additional information for the early identification of patients at higher risk, in particular those aged $\geq$75 years[6] (Table 2). EF $<$ 40%, together with age $>$ 70 years and the presence of a physical stressor, are the three criteria in the Mayo Clinic risk score for acute heart failure in TTC.[23] Elderly patients demonstrate significantly delayed and lower LV systolic function recovery compared with younger patients.[6]

Extensive apical myocardial dysfunction and reduced intraventricular systolic flow velocity are predisposing factors for thrombus formation. Mural or pedunculated thrombi can be visualized at the apex in 1% to 2% of patients with TTC during the first 2 days, causing stroke or systemic embolization (renal or lower limb embolism) in