Microvascular Dysfunction in Takotsubo Cardiomyopathy

Shreyas Gowdar and Lovely Chhabra

Dept. of Cardiovascular Medicine, Hartford Hospital, University of Connecticut School of Medicine, Hartford, CT, USA (06102)

Corresponding author:
Lovely Chhabra, MD
Dept. of Cardiovascular Medicine, Hartford Hospital, University of Connecticut School of Medicine, Hartford, CT, USA
80 Seymour Street, Hartford, CT (06102)
Email: lovids@hotmail.com

Abstract

Takotsubo cardiomyopathy or stress-induced cardiomyopathy, is characterized by transient cardiac dysfunction, usually but not always triggered by physical or emotional stress. Takotsubo cardiomyopathy may mimic an acute coronary syndrome due to an overlapping presenting clinical spectrum. Typically, apical involvement with hypercontraction of basal left ventricle (apical type) is predominant, but atypical types involving basal, midventricular, and right ventricular myocardium have also been described. To date, the exact pathogenic mechanism of this disease remains unclear, however, sympathetic or catecholaminergic hyperactivity, multivessel coronary vasospasm, microcirculatory disorder, and estrogen deficiency have been proposed to be the likely underlying pathogenic mechanisms. In this review, we specifically highlight the association of microcirculatory dysfunction in takotsubo cardiomyopathy which has been more recently recognized as an important pathogenetic contributor to this disease.

Keywords: Microvascular dysfunction; Takotsubo Cardiomyopathy; Myopericarditis

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Introduction

Takotsubo cardiomyopathy (TC), also called stress cardiomyopathy, apical ballooning syndrome or broken heart syndrome, is a syndrome characterized by transient regional systolic dysfunction of the left ventricle (LV), mimicking myocardial infarction (MI), but in the absence of evidence of angiographic significant obstructive coronary artery disease (CAD) or acute plaque rupture. In most cases of TC, the regional wall motion abnormality extends beyond the territory perfused by a single epicardial coronary artery. The systolic apical ballooning appearance of the LV is the most typical form of this syndrome associated with mid and apical segmental hypokinesis and hyperkinesis of the basal walls. The first case of TC was described in 1990 in Japan and since then, this syndrome has been increasingly recognized around the globe.1 Despite abundant research, the exact pathogenic mechanism of this disease remains elusive to date.2 Several postulated mechanisms for its pathogenesis have been described which include sympathetic or catecholaminergic hyperactivity, multivessel coronary vasospasm, microcirculatory disorder, and estrogen deficiency. Microvascular dysfunction (MVD) in particular has been recognized as an important pathogenetic contributor to the causation of TC in the more recent years and remains the focus of discussion in this review.

MVD refers to the impairment of the delivery of blood to the myocardium due to one or more pathologic conditions occurring at the level of the pre-arterioles, arterioles, or capillaries in the setting of normal epicardial coronary arteries. Four main types of MVD have been described on the basis of the clinical setting in which it occurs:

(a) MVD in the absence of myocardial diseases and obstructive coronary artery disease (CAD),
(b) MVD in myocardial diseases,
(c) MVD in obstructive CAD, and
(d) iatrogenic MVD.2 In TC, type-1 microvascular dysfunction occurs as it essentially occurs in the absence of a primary myocardial disease process and obstructive CAD.

Assessment of coronary microvascular function:

Microvascular function is evaluated by testing vascular flow responses to vasodilator stimuli using various techniques (invasive and non-invasive). The normal response to administration of vasodilator stimuli is coronary microvascular relaxation resulting in an increase of coronary blood flow. In contrast, patients with endothelial dysfunction often exhibit reduced dilation or even coronary microvascular constriction. Coronary flow reserve (CFR) serves as an objective marker for microvascular function and is defined as the ratio between hyperemic and basal coronary flow. The most widely used substances are adenosine and dipyridamole, to test endothelium-independent vasodilatation and acetylcholine is used to test endothelium-dependent response. A CFR below 2.5 is usually considered the most accepted marker of MVD, although variable thresholds have been used in different studies.3

The current gold standards for clinically assessing microvascular function have been CFR using invasive testing and myocardial...
perfusion reserve (MPR) using positron emission tomography (PET) or cardiac magnetic resonance imaging (CMR) analysis.

Invasive techniques: Quantitative coronary angiography can be used to directly and invasively examine the change in diameter in response to intracoronary infusions of endothelium-dependent vasodilators such as acetylcysteine. A similar method, though based on different physical properties to test coronary microcirculatory function, utilizes thermodilution and index of microcirculatory resistance. This technique is similar to pharmacological- and pressure-based techniques, but instead uses intracoronary temperature measurements to approximate flow. Thermodilution and intracoronary Doppler (ICD) flow wire allow coronary blood flow and CFR quantification. Use of Intravascular Doppler Ultrasonography (IVDUS) permits a direct visualization of the arterial walls and detection of atherosclerotic plaques. It is commonly used for intracoronary recording of coronary blood flow by doppler and pressure wires. Intracoronary Doppler is the most commonly used technique as it allows a direct measurement of coronary flow velocity in epicardial coronary arteries. The product of coronary flow velocity and the cross-sectional arterial area gives a measure of coronary blood flow. Evaluations prior and post vasodilator infusion allows measurement of CFR. When intracoronary doppler and pressure sensors are incorporated, it is possible to calculate the index of microvascular resistance (IMR) which is defined as the distal coronary pressure multiplied by the hyperemic mean transit time (hTmn). Angiography also allows evaluation of microvascular function indirectly through the use of some obtained angiographic indexes, namely myocardial blush grade (MBG) and TIMI frame count (TFC). Myocardial blush is the myocardial opacification resulting from the injection of dye into the coronary artery. Counting the number of heart cycles required for it to fade out gives the Myocardial Blush Grade (MBG), which depends on the microcirculation resistance to the dye passage and the efficiency of venous drainage. Total myocardial blush score is the sum of the MBG of each coronary territory and defines the overall microvascular functionality.

TFC is defined as the number of cineframes required for contrast to reach a standardized distal coronary landmark in the culprit vessel. The number is usually expressed based upon a cinefilming rate of 30 frames/second. Thus, a frame count of 30 would mean that 1 second was required for dye to traverse the artery. A correction factor is used in calculating the TFC depending on the vessel length. It is related to the index of microvascular resistance and the velocity wherewith the dye fills the epicardial vessels. Thus, similar to MBG, total TFC is the sum of the three major coronary vessel scores and is useful for a comprehensive view of the coronary microcirculation function.

Non-invasive techniques: The advent of noninvasive techniques such as PET and CMR increase the feasibility of diagnosing MVD while removing the risk associated with catheter based techniques. PET perfusion imaging has shown a linear relationship between myocardial blood flow (MBF) and radioisotope signal intensity, allowing highly accurate myocardial blood flow quantification. Doppler transthoracic echocardiography has also gained some acceptance in the published data as well as reproducibility in populations especially with known CAD. However, this technique suffers the limitation of variability in patient anatomy and the inability to evaluate multiple coronary vascular territories. It mainly allows the measurement of CBF velocity in the left anterior descending artery.

Pathogenesis and association of MVD in TC:
By definition, patients with Takotsubo syndrome do not have obstructive CAD, yet they demonstrate abnormal myocardial perfusion, abnormal coronary flow reserve measured by echocardiography, and abnormal PET imaging, consistent with an inverse perfusion/metabolism mismatch. Myocardial perfusion, contractility, and left ventricular function improve markedly with the administration of intravenous adenosine in patients with TC, but not in those with acute myocardial infarction, while patients with a history of TC demonstrate cold pressure test-induced wall motion abnormalities. Furthermore, a long-term follow-up study demonstrated reduced endothelial-dependent response to acute mental stress in patients with a history of TC. Taken together, these observations suggest that the syndrome is caused by intense microvascular constriction with subclinical MVD persisting over time, perhaps facilitated by endothelial dysfunction.

Materials and Methods:
We searched PubMed/Medline, Scopus and Google scholar for original articles published between 1990 and 2015, focusing on takotsubo cardiomyopathy and microvascular dysfunction. The search terms used, alone or in combination, were “takotsubo cardiomyopathy”, “stress cardiomyopathy”, “apical ballooning syndrome”, “pathogenesis”, “microvascular dysfunction”, “risk factors”, “microvascular function” and “coronary endothelial dysfunction”. All English-language articles were then identified and independently reviewed in details. Papers included were original research, reviews, case reports and relevant correspondences. After a comprehensive review of the articles selected, we used the relevant literature for our current discussion.

Results and Discussion:
Although MVD is quite well reported in the context of microvascular angina or chest pain syndromes, it is relatively less well described in context of TC. There is however a growing evidence suggesting an association between MVD and TC. Many experts believe that MVD may not be a distinct contributor for the disease and instead may be a co-association of the main pathogenesis and imparts only a small pathogenic contribution. For instance, there are beliefs that an exaggerated sympathetic stimulation with regional cardiac sympathetic disruption may be associated with catecholamine overload with resultant spillover and catecholamine-induced myocarditis and microvascular dysfunction. Thus, whether MVD is the causative factor or a consequence of this disorder remains elusive.

Studies utilizing noninvasive means such as Doppler transthoracic echocardiography have demonstrated impairment of microvascular dysfunction early in the course of the disease with recovery noted in a few weeks to months. Collste et al. in a study comprising 22 patients demonstrated statistically significant reduction in CFR at a low dose dobutamine (10 μg/kg/min) based stress testing in TC patients when compared with healthy controls. Studies have also used TFC for evaluation of microvascular function in TC patients and have demonstrated conflicting results. Bybee et al. noted abnormal TFC during acute phase of TC in all patients and this was present in all three coronary vessels. Their findings suggested that diffuse impairment of coronary microcirculatory function may play a role in the underlying etiopathogenesis although it remained unclear if microvascular dysfunction is the primary cause or a secondary phenomenon.
Invasive measurements of MVD in TC- TIMI Frame count (TFC)

TFC has been advocated as a simple and inexpensive quantitative measure of coronary flow reserve, for all three major epicardial coronary arteries. TFC refers to the number of frames required for contrast material to travel from the coronary ostium to the standardized distal landmark. Corrected TFC involve a correction factor applied to the left anterior descending artery (LAD), to account for the longer length of the LAD compared to the right coronary and left circumflex arteries. TFC has been used as a marker of endothelial and microcirculatory dysfunction in TC. A retrospective study by Khalid et al, compared TFC in 16 patients with TC with 15 controls with normal coronary angiograms.

The mean corrected TFC in the LAD of TC patients was higher than those of the controls (19.61 ±5.77 vs 16.65 ± 2.41, p=0.04). The mean TFC in the left circumflex and right coronary arteries were not statistically different between the TC cases and controls (18.93 ± 3.87 vs. 18.06 ± 3.95; p=0.27 in left circumflex and 20.13 ±3.70 vs. 19.13 ±4.22; p=0.25 in right coronary artery, between TC cases and controls, respectively). The mean corrected TFC was higher (by 3 frames/sec) in the LAD of TC patients as compared to the control population, indicating presence of microvascular or endothelial abnormalities in the LAD territory. The authors postulated that this could potentially explain the presence of left ventricular apical dysfunction with sparing of the basal segments, in patients with TC.

On the contrary, higher TFCs were noted in all three coronary artery territories in the acute phase of TC in a study by Bybee et al, which suggested diffuse coronary microcirculatory abnormalities. In this study, the TFC from admission coronary angiograms of 16 female patients with TC were compared with the TFC of 16 age and gender matched control cohort who had normal coronary angiograms preceding valve surgery. All patients with TC had abnormal TFC (>30 cineframes/second) in 1 or greater epicardial coronary vessels. Ten out of 16 patients (62.5%) had significantly abnormal TFCs in all three epicardial coronary vessels. The mean TFCs were higher in all three major epicardial coronary arteries in the TC patients compared to the controls. (Corrected LAD= 41 ± 11 vs. 24 ± 4 cineframes; left circumflex= 44 ± 14 vs. 27 ±6 cineframes; and right coronary artery= 35 ± 12 vs. 25 ± 5 cineframes; p <0.001).

Two patients underwent repeat angiography within 28 days after initial presentation, which revealed normalization of the TFCs in both patients in all three epicardial vessels. These findings revealed increased microcirculatory resistance and diffuse CMVD, highly suggestive of CMVD playing a major role in pathogenesis of TC. Another study by Kurisu et al evaluated TFCs in 28 patients with TC and compared to 20 controls with atypical chest pain that had normal angiograms, and showed similar results. The angiograms were recorded at 25 frames/ second on a 35 mm cine frame. TC patients had significantly elevated TFCs in all three epicardial coronary arteries, compared to controls, in the acute phase. (LAD corrected count of 63 ± 24 vs. 28 ± 7, left circumflex frame count of 42 ± 15 vs. 20 ± 6, right coronary frame count 48 ± 16 vs. 25 ± 5, in TC patients vs. controls, respectively).

In subsequent follow up angiography in 20 patients at a mean of 11 ± 4 days after initial presentation and after resolution of LV dysfunction, the TFCs showed an interval decrease in all patients when compared with the acute phase, but remained persistently higher when compared to controls (LAD corrected count of 47 ±13, LCX frame count of 36 ± 10 and RCA frame count of 37 ± 8). Similarly, Barletta et al, in a study of 17 patients, demonstrated abnormal, elevated corrected TFCs >28 in 88% of patients, with 7 patients with single vessel involvement, 2 patients with 2 vessel involvement and 6 patients with 3 coronary vessel involvement. Taken together, these studies compellingly indicate that impaired CMVD may be a major component of the pathogenesis of TC, although it remains difficult to definitely ascertain whether CMVD has an etiologic association or whether it is a secondary phenomenon, resulting from TC.

TFCs are a measure of endothelial and microvascular dysfunction and a marker of perfusion, and can thus be a useful index for assessing microvascular dysfunction in TC. Notably in another study TFCs on 56 patients with TC were compared to 20 female patients with no significant CAD on angiography. TFCs were higher in the LAD of TC patients vs. controls (25 ± 12 vs. 20 ± 10 frames, P=0.05) and, in the left circumflex (29 ± 13 vs. 22 ± 7 frames, P <0.01) and were not statistically significantly different in the right coronary artery. In patients with TC, TFCs in all 3 coronary arteries were also not different between those with ST elevation compared to those without ST elevation. In patients with TC, markedly prolonged TFCs >30 in 1 coronary artery were seen in 34% of patients, in 2 coronary arteries in 21% of patients and in all three coronary arteries in 5% of patients.

There was no significant difference in the frequency of markedly elevated TFCs in the TC patients with ST elevation compared to those without ST elevation. However, there were modest elevations in the TFCs in the TC patients compared to controls. The authors however concluded that given the variability in the frame counts, microvascular dysfunction was not likely to be a significant player in the pathophysiology of TC. However, their data did demonstrate modest prolongation in TFC in two coronary vessels (LAD and left circumflex) of TC patients compared to controls which was statistically significant, and given that 60% of the TC patients had markedly prolonged TIMI frame counts >30 in one or multiple coronary arteries, microvascular dysfunction as a determinant of TC remains certainly plausible.

Invasive measurements of CMVD- TIMI myocardial perfusion grade (TMPG)

TIMI myocardial perfusion grade (TMPG) is an established surrogate marker of myocardial perfusion and has been well validated in acute coronary syndrome patients. A large case series by Elseber et al evaluated TMPG in 42 patients with TC and 14 control patients. Coronary angiograms were performed within 24 hours of presentation and myocardial perfusion grade was quantified as grade 0 (absent perfusion), grade 1 (dyed stains the myocardium and persists in the next injection), grade 2 (dye enters myocardium but washes out slowly and is strongly persistent at the end of the injection) and grade 3 (normal entry and exit of dye in myocardium). Out of 42 patients with TC, 69% (29) had abnormal TMPG, and 13 had normal TMPG. Of the 29 patients with abnormal TMPG, 18 had abnormal perfusion in all 3 coronary artery territories, 7 had abnormal myocardial involvement in 2 coronary artery territories, and 4 had abnormal perfusion of myocardium in 1 coronary artery territory. The abnormal perfusion in all 29 patients involved the apex and mid ventricular myocardium, and 18 patients had TMPG of 2, nine had TMPG of 1, and 2 patients had severe TMPG abnormalities, with grade 0. All 29 patients with abnormal TMPG had no significant epicardial coronary obstruction. All of the control patients had low left ventricular ejection fraction (LVEF) (mean 39%) and normal TMPG. Patients with TC with abnormal TMPG had higher mean levels of peak troponin (0.84 ± 0.68 vs. 0.42
and independent microvascular dysfunction, with the magnitude of microvascular vasomotor function in response to ACh and adenosine. In the two patients with recurrence of TC, Kume et al. evaluated CFV and CFVR on angiography within 24 hours of symptom onset and after 3 weeks. The phasic CFV spectrum using a doppler guidewire was measured in the middle of the LAD, the left circumflex and the right coronary artery at rest and at peak hyperemia, after intravenous administration of adenosine at 0.15 mg/kg/min.

Using computerized planimetry, the time averaged instantaneous peak velocity (APV, cm/s) during one cardiac cycle and the systolic and diastolic APV and the diastolic/systolic APV ratio were measured from phasic CFV recordings. Deceleration time of diastolic velocity (DDT in ms) was measured from the ratio of APV at maximal hyperemia to the APV at rest. CFVR of all three coronary arteries were reduced in all patients during the acute phase, with mean values of 1.7 ± 0.5 in LAD, 1.7 ± 0.5 in left circumflex and 1.7 ± 0.3 in RCA. The CFVR significantly increased in all the three epicardial coronary arteries at the 3 week follow up angiography, with mean CFVR values of 2.4 ± 0.5 in LAD, 2.7 ± 0.8 in left circumflex and 2.5 ± 0.4 in RCA. Similarly the DDT was low during the acute phase in all three coronary arteries, with values of 450 ± 176 ms in LAD, 446 ± 232ms in left circumflex and 491 ± 86 ms in RCA.

The DDT was significantly higher at the 3 week follow up, with DDT of 1,027 ms ± 142 in LAD, 796 ms ± 194 in left circumflex and 822 ms ± 230 in RCA. The CFVR and DDT values during the acute phase demonstrated significant correlation. Thus, the LV wall motion and both CFVR and DDT recovered to normal in all patients in all three coronary arteries. As the CFVR and DDT are measures of coronary microvascular dysfunction in stable hemodynamic conditions and in absence of epicardial stenosis, this study revealed diffuse microvascular impairment in all three coronary artery distributions in the acute phase of TC, with marked improvement at 3 weeks, along with normalization of LV wall motion. This would suggest coronary microcirculation dysfunction is a likely contributing factor in the pathogenesis of TC.6

On the other hand, Abe et al reported no significant coronary microvascular dysfunction in a case series comprising of only 3 patients who underwent invasive intracoronary doppler guidewire testing.4 The authors reported no significant impairments in CFR (ranging from 1.8 to 3.6) and DDT (deceleration time of diastolic flow velocity (>600msec) and diastolic to systolic velocity ratio (DSVR), in the acute phase of TC.4

Invasive methods of CMVD - intracoronary doppler

Intracoronary Doppler flow techniques use doppler tipped wires to measure intracoronary blood flow velocity and arterial cross sectional area to estimate the coronary blood flow. Coronary flow velocity (CFV) pattern and coronary flow velocity reserve (CFVR) are indices of coronary microvascular dysfunction, and are measured using intracoronary doppler guidewire during coronary angiography. In a study of 8 patients with TC, Kume et al evaluated CFV and CFVR on angiography within 24 hours of symptom onset and after 3 weeks.5 The phasic CFV spectrum using a doppler guidewire was measured in the middle of the LAD, the left circumflex and the right coronary artery at rest and at peak hyperemia, after intravenous administration of adenosine at 0.15 mg/kg/min.

Invasive measurements of CMVD - intracoronary doppler and vasomotor function testing

Invasive direct measurements of coronary epicardial and microvascular vasomotor function testing in response to pharmacologic agents have also been quite well validated as a measure of microvascular dysfunction. In a study by Patel et al, data from 10 patients with TC that underwent invasive coronary vasomotor testing done at a median of 152 days after their initial presentation were analyzed.6 Coronary vasomotor testing was done with three different doses of acetylcholine (ACh) to assess endothelium dependent vasomotor function, and with adenosine to evaluate endothelium independent vasomotor reactivity. Out of the 10 patients, the median change in coronary artery diameter after intracoronary ACh administration was -9.3%, with 60% of patients demonstrating epicardial vasoconstriction, in response to intracoronary ACh administration, and 30% displaying severe dysfunction, with >20% vasoconstriction.

The rest of the patients had only modest vasodilatation with ACh. The median increase in coronary blood flow (CBF) with adenosine was 13.1% in the TC patients, compared to a median CBF increase of 103% in a large cardiac risk factor profile matched control group. Seventy percent of patients had <50% increase in CBF after ACh infusion, and 30% of all patients had severe impairment of CBF. Seventy percent of the patients demonstrated at least one abnormal measure of vasomotor dysfunction in response to adenosine, with 50% showing severely impaired vasomotor response in either epicardial or microcirculatory level. With intracoronary adenosine infusion, 60% of the TC patients had a significantly low coronary flow reserve (CFR) below the normal cutoff of 2.5, with median CFR of 2.2.

Overall, 90% of patients had at least one abnormal measure of microvascular vasomotor function in response to ACh or adenosine. In the two patients with recurrence of TC, peak change in CBF and endothelium independent CFR was significantly lower than those without the recurrence. In summary, this study found that a great majority of patients with TC that were analyzed had impaired or abnormal coronary vasomotor response to intracoronary ACh and adenosine, with 90% of patients showing evidence of endothelium dependent and independent microvascular dysfunction, with the magnitude of vascular dysfunction greater in the microcirculation than in the epicardial coronary vasculature.6

Invasive methods of CMVD - Index of Microvascular resistance (IMR)

In a study by Layland et al, the authors reported a catheter based evaluation of microcirculatory function.7 Using a temperature and pressure sensing guidewire, the mean transit time, which is a surrogate of coronary blood flow, is calculated by obtaining three reproducible thermodilution curves, by injecting 3 ml

\[ \pm 0.33 \text{ ng/ml, } p=0.047 \] and also had more significant ECG changes of ST elevation or deep T wave inversions than those with normal TMPG (86% vs. 46% respectively, p=0.006). Of significant interest, the two patients with TMPG score of 0 had ST elevations and TIMI grade-3 flow in all epicardial coronary arteries.

This study indicates the presence of abnormal microvascular function as evidenced by abnormal perfusion with abnormal TMPG, in the acute phase of TC. The degree of myocardial injury as measured by ECG changes of ischemia and peak troponin level correlated with the severity of microvascular dysfunction, as measured by abnormalities in TMPG. These findings strongly suggested that microvascular dysfunction causing perfusion impairment and resultant myocardial stunning is an extremely plausible pathophysiologic explanation of TC, and this could be precipitated by a catecholamine surge. Furthermore, the impaired microvascular function in Takotsubo patients was suggested to be likely a primary cause of the cardiomyopathy, rather than a secondary phenomenon, given that the control patients had similar magnitude of left ventricular dysfunction and higher filling pressures, and yet had normal microvascular perfusion (normal TMPG).17

International Cardiovascular Forum Journal 5 (2016) DOI: 10.17987/icfj.v5i0.222

Reviews | 43
saline at room temperature into a coronary artery at peak hyperemia. Intracoronary pressures distal to the stenosis are also measured at peak hyperemia. The Index of microvascular resistance (IMR) is obtained by multiplying the pressure by the mean transit time. In this study, the IMR in both the LAD and RCA of the TC patient in the acute phase, were elevated at 45U and 37U, respectively. Repeat measurements 6 weeks later showed significant reductions in the IMR in the LAD and RCA, at 21U and 24U, respectively, and this corresponded to resolution of LV dysfunction.

This indicates higher microcirculatory resistance in the acute phase of TC, with normalization during the recovery phase. This may imply a global microvascular dysfunction in TC, given elevation of IMR in different vascular territories. Possible mechanisms of elevated IMR include catecholamine excess induced alpha receptor stimulation in resistance vessels, causing diffuse vasoconstriction. Another report of a 56-year-old male with recurrent TC with normal coronary angiography described results of measurement of resting and hyperemic microvascular resistance using the thermodilution method. After intracoronary infusion of papaverine, the IMR was elevated at 29.1 mm Hg/ sec (normal value <20 mmHg/sec) and CFR was significantly reduced at 1.8 (Normal CFR>3) and the FFR was 0.96, confirming the absence of epicardial stenosis. This highlights the abnormal recruitability of coronary microvascular vasodilatation, increased microvascular resistance and diminished CFR, in the acute phase of TC, and these factors likely cause impaired myocardial perfusion and ischemia causing myocardial stunning.

Noninvasive methods of CMVD assessment— Transthoracic Doppler Echocardiography

Transthoracic doppler echocardiography (TDE) measurements of CBF can be used as a noninvasive bedside tool for assessing CMVD. The ratio of peak CBF at maximal vasodilation in response to adenosine or dipyridamole to the CBF at rest is used as a measure of coronary microvascular vasodilatory function. Ratios <2.0 would be a strong indicator of CMVD.

A report by Meimoun et al described the use of transthoracic doppler echocardiography (TDE) after adenosine infusion over 2 minutes, in a patient with TC, to evaluate the distal LAD flow. The mean CFR within 24 hours of presentation was low, at 2.1. Repeat TDE after 4 weeks showed significantly improved CFR, at 2.7, with normalization of LV wall motion abnormalities. After 3 months, repeat CFR was measured at 3.0. This highlights the transient coronary microcirculatory impairment with subsequent improvement/resolution. In another study by the same author, distal LAD flow was assessed within 12-24 hours of admission in 28 patients admitted with TC and was compared to 28 patients with acute MI. The blood flow velocity was assessed by pulse wave Doppler, and CFR (ratio of hyperemic to basal peak diastolic flow velocity) was evaluated after adenosine infusion over 2 minutes. The sensitivity and specificity of diagnosing TC were 100% and 64% respectively, with a high diagnostic accuracy of 82%. The sensitivity, specificity and diagnostic accuracy of pattern of wall motion abnormality were 75%, 96% and 86%, respectively. Of the acute MI patients, 50% had proximal LAD pattern of wall motion abnormality were 75%, 96% and 86%, of 82%. The sensitivity, specificity and diagnostic accuracy of CFR (ratio of hyperemic to basal peak diastolic flow velocity) was evaluated after adenosine infusion over 2 minutes. The sensitivity and specificity of diagnosing TC were 100% and 64% respectively, with a high diagnostic accuracy of 82%.

The CFR was higher in the TC patients compared to the acute MI patients, despite revascularization (P<0.01). No-reflow pattern was not seen in any TC patients but was present in 32% of acute MI patients. The authors proposed a cut off CFR value of 1.8 to distinguish between TC and acute MI patients, with TC patients having CFR>1.8. Thus, the authors found impaired CFR in both TC and acute MI patients; however the CFR was less impaired in the TC group. The higher CFR in the face of lower wall motion score index in TC patients implies that factors other than microcirculatory impairment also play a role in TC pathogenesis.

However, some studies have shown conflicting results. Sganzerla et al evaluated 5 patients with TC with no concomitant medical conditions by transthoracic pulse wave doppler echo to evaluate distal LAD perfusion in the acute phase of TC, and they were compared to five age, sex and ejection fraction matched controls. Mean and peak diastolic flow velocities, velocity time intervals were recorded at baseline, during peripheral venous adenosine infusion and at recovery. Coronary flow reserve (CFR) was calculated by dividing the peak maximum hyperemic value with the resting value. A CFR of >2.0 was considered normal. In all 5 cases of TC, CFR calculated by velocity time interval (VTI mean 2.54 ± 0.13) and by average diastolic peak blood flow velocity (Mean CFR 2.42 ±0.08) was over the cutoff of 2.0, indicating normal coronary flow reserve and these were not different from the controls. These normal CFR values were seen in the TC patients with no history of hypertension, diabetes, dyslipidemia and smoking. The authors hypothesized that conorbid conditions such as hypertension and diabetes mellitus may be responsible for impaired CFR as seen in other studies of TC patients. Thus, they speculated that MVD is not a significant factor in pathogenesis of TC, but rather may be a consequence of concomitant medical conditions that can cause impaired CFR.

Noninvasive methods- myocardial contrast echo (MCE)

Myocardial contrast echocardiography employs the injection of gas filled microbubbles that, due to very small radii (<5µm), effectively scatter ultrasound. This scattered ultrasound is quantified using video intensity (VI) to evaluate capillary flow and density. After obtaining a steady state of contrast infusion, a pulse of high energy ultrasound is given and low mechanical index imaging is done to assess rate of reappearance, which is a marker of RBC velocity. Change in VI with time is plotted onto a curve that represents replenishment phase of contrast flow, and A and B values are obtained, with A representing microvascular cross sectional area and myocardial blood volume (MBV) and B representing myocardial blood flow velocity. In a study by Galuoto et al, 15 patients with TC and 15 control patients with STEMI with LAD thrombotic occlusion were evaluated with myocardial contrast echocardiography, within 3 ± 2 days of presentation. Myocardial perfusion and contractility were evaluated at baseline, after adenosine infusion, at peak hyperemia and repeated at 1 month follow up. Regional wall motion was semi-quantitatively assessed, with scores of 1= normal, 2= hypokinesia and 3= akinesia in all myocardial segments, and a wall motion score index was derived by the sum of scores in all segments divided by the number of segments. Myocardial contractility defect length was evaluated by measuring wall motion defect length (WMDL), which is obtained from endocardial length of wall motion abnormality, averaged from each apical view and expressed as WMDL/LV endocardial length x 100. Myocardial opacification was also semi-quantitatively scored in all 16 segments using scores of 1 to 3, with 1 being normal, 2 being reduced and 3 indicating absent opacification, and a contrast score index (CSI) was obtained by the sum of all segment scores divided by the number of segments. Myocardial perfusion
defect length was assessed by using contrast defect length (CDL), which is a measure of length of endocardial perfusion abnormality, and then expressed as CDL/LV x 100. All of the TC patients and STEMI patients had a perfusion defect in the region of myocardial dysfunction, in the apical segments in the TC patients, with transmural involvement in a majority (72%) of apical ballooning syndrome patients.

Perfusion significantly improved in the apical segments during adenosine infusion in the TC patients, as seen by increased CSI (1.48 ±0.17 vs. 1.28 ± 0.17 at baseline, P < 0.001) and CDL (22.7 ±5.9 vs. 14.8 ±7.1% at baseline of LV endocardial length; P < 0.001), but did not change in the STEMI patients. The perfusion rapidly returned to baseline impaired perfusion in the TC patients, after cessation of adenosine infusion. At the 1 month follow up, myocardial perfusion had significantly improved, with significantly increased CSI (1.00 ±0.02, P < 0.001 vs. baseline) and CDL (0.7 ±2.0% of LV endocardial length vs. baseline, P < 0.001) in the TC patients, with 86% of TC patients demonstrating normal perfusion. The STEMI patients had no significant change in myocardial perfusion at 1 month. In both the TC and STEMI patients, regional myocardial wall motion dysfunction was significantly greater than the perfusion defect, with higher WMDL compared to CDL (WMDL 35.7 ±12.8 vs. CDL 22.7 ±5.9% of LV endocardial length in TC patients, P = 0.001 and WMDL 41.3 ±12.8 vs. CDL 23.7 ±8.3% of LV endocardial length, P <0.001, in STEMI patients). Regional wall motion abnormalities improved during adenosine infusion compared to baseline, as seen by lower WMSI (1.79 ±0.24 to 1.51 ±0.28, P <0.001) and lower WMDL (35.7 ±12.8 to 26.2 ±13.0% of LV endocardial length, P <0.001) in the TC patients, and promptly returned to baseline after cessation of adenosine. However in the STEMI patients, there was no significant change in wall motion abnormalities after adenosine challenge, with no change in WMSI (from 1.93 ±0.22 to 1.92 ±0.23, P = 0.93) and WMDL (from 41.3 ±12.8 to 42.0 ±12.2% of LV endocardial length, P = 0.88).

Adenosine infusion resulted in transient significant decrease in LVESV in TC patients but not in acute STEMI patients. At 1 month follow up, in the TC patients, myocardial contractility was significantly improved, (WMSI 1.03 ±0.05 compared to baseline, P <0.001 and WMDL 1.7 ±3.9% of LV endocardial length, P <0.001 vs. baseline) in congruence with improvement in perfusion, and was in parallel with lower LVESV and marked improvement in LVEF. There was no improvement in regional wall motion contractility or in LVEF in STEMI patients, along with no improvement in perfusion. This study shows reversible microvascular dysfunction in TC patients, but not in those with STEMI, as seen by perfusion defects in the dysfunctional myocardial regions, with transient improvement during adenosine administration, and significant improvement in myocardial perfusion at 1 month, reflected in resolution of myocardial wall motion dysfunction.23 This microvascular constriction, with improvement with adenosine, likely reflects a functional change in microvascular dysfunction, as opposed to anatomical changes in coronary microvasculature, which would be insensitive to adenosine administration, and would remain unchanged over time. The myocardial dysfunction also is solely related to microvascular perfusion defect, since adenosine induced recovery of coronary microvascular perfusion resulted in significant improvement in myocardial dysfunction.23 Thus, the pathogenesis of TC involves a multi-territorial reversible coronary microvascular vasoconstriction, causing impairment in perfusion and leading to myocardial dysfunction, with recovery of microvascular function with adenosine and after the acute phase.23

Abdelmoniem et al evaluated qualitative and quantitative parameters of myocardial perfusion using MCE and compared segments with normal perfusion to those with dysfunctional wall motion, in 9 patients with TC, with normal epicardial coronary vessels on angiography.22 MCE was performed at a mean 16.9 ±11.9 hours after coronary angiography, using destruction-replenishment technique, with high mechanical index (1.2) flash (5-10 frames) followed by low mechanical index (0.2) imaging for 10-15 cardiac cycles. All 9 patients had segmental wall motion abnormalities, with mean WMSI (wall motion score index) of 1.93 ±0.43 and mean LVEF of 40 ±9%. Eight patients had left ventricular apical wall motion dysfunction while 1 patient had midventricular wall motion abnormalities with apical sparing.

Significantly lower myocardial blood flow velocity (β) and lower myocardial blood flow (Aβ or myocardial blood flow index) were seen in segments with dysfunctional wall motion compared to those with normal wall motion. Perfusion defects were congruent with wall motion dysfunction in 71% of segments. Out of those segments with discordance between qualitative perfusion and wall motion, the quantitative parameters of β and Aβ were significantly lower in segments with dysfunctional wall motion compared to those with normal wall motion (β =0.22 ±0.20 vs. 1.79 ±0.57, P =0.01; Aβ = 1.90 ±1.1 vs. 24.29 ±19.9, P =0.02). In all patients, there was recovery of wall motion on follow up echocardiogram at a mean of 60.3 ±66 days. This study demonstrated abnormal myocardial perfusion detected by qualitative MCE and confirmed by quantitative MCE, associated with segments with abnormal wall motion dysfunction, in the acute phase of TC, demonstrating severe microvascular dysfunction in the acute phase of TC patients.22

Jain et al utilized myocardial contrast echo to evaluate myocardial perfusion in 9 patients with TC, within 24 hours of presentation, again within 1 week, and then at 3-6 months.24 Intravenous contrast for myocardial opacification was followed by image acquisition using destruction-replenishment technique, with continuous low power imaging at Mechanical index (MI) of 0.1 and intermittent pulse disruption of microbubbles with high power with mechanical index >1. Perfusion was determined by visual estimation of the number of cardiac cycles required to refill each myocardial segment, after bubble disruption, with segmental opacification in <4 cycles defined as preserved microcirculatory function and opacification in >4 cycles defined as abnormal microcirculation. The mean LVEF of all patients improved from 38% ±9% at admission to 48% ±9% in one week to normal LVEF (67% ±3%) at 3-6 months. In the acute phase, abnormal perfusion was seen with average number of wall segments with absent perfusion in 4 ±1.7 segments. At 1 week follow up, average number of wall segments with absent perfusion had decreased to 2 ±1.6 and at 3 to 6 months, myocardial perfusion was normal in all patients except one patient, who had 1 segment with >5 cycles required for opacification. At 1 week, relative myocardial perfusion in the TC patients had improved by 50% while mean LVEF had improved by 26%. This study demonstrated complete absence of myocardial perfusion in the apical segments and reduced perfusion in the mid ventricular segments, and improvement of myocardial perfusion occurred prior to improvement of regional wall motion abnormalities, suggesting that restoration of microcirculatory dysfunction is essential to recovery of myocardial wall motion dysfunction.24

In a case series of TC by Alfonso et al, 3 patients with TC were evaluated with MCE to estimate myocardial blood flow and perfusion kinetics and speckle strain imaging was used to assess regional contractile dysfunction.25 In the first patient
Noninvasive methods of CMVD assessment - PET perfusion imaging

Noninvasive methods of evaluating microvascular function include assessing myocardial flow reserve using PET or CMR. PET perfusion imaging is fast becoming a widely accepted measure of CMVD. It provides an accurate quantitative measure of myocardial blood flow as it is linearly related to radioisotope signal intensity.24

In a study of 3 patients with TC, Feola et al evaluated myocardial perfusion and myocardial blood flow using PET imaging.25 All 3 patients underwent coronary angiography at admission which ruled out significant coronary stenosis. PET perfusion imaging using N13 ammonia at rest and during pharmacologic stress with adenosine and metabolic imaging using FDG was done within 3 days of presentation and again at 3 months of follow up. In the acute phase of TC, all 3 patients demonstrated apical enlargement and severe reduction in FDG uptake in the apical and midventricular segments, indicating severely impaired metabolism, and on N13 ammonia perfusion imaging, had normal tracer uptake at rest with only a slight reduction in perfusion at the apex post adenosine stress. This was characteristic of an inverse flow/metabolism mismatch pattern.

At 3 months of follow up, with normalization of LV function, all 3 patients had resolution of apical dilation, and had normal FDG uptake at the apex, and normal N13 ammonia uptake at the apex, at rest and after adenosine stress, indicating normal apical metabolism and perfusion. In the acute phase of TC, CFR was reduced in the apical segments in all patients, and in the midventricular segments in 2 patients, compared to basal segments. The CFR significantly increased in the apical and midventricular segments on PET imaging at the 3 month follow up evaluation. The MBF assessed by PET imaging was significantly reduced in the apical segments in the acute phase in comparison to the midventricular and basal segments, and remained reduced in 2 of the 3 patients after 3 months. Cardiac MRI on all patients during acute phase and 3 month follow up showed no evidence of delayed gadolinium enhancement, indicating absence of myocardial necrosis during acute phase and follow up. These results indicate that the pathogenesis of TC involves transient metabolic dysfunction at the cellular level, with reduced myocardial glucose uptake at the apex, corresponding to impaired CFR at the apex. The LV dysfunction, impaired glucose uptake and reduced CFR demonstrated reversibility at 3 months, likely due to resolution of microvascular dysfunction.26 In another case report by Feola of a 65 year old woman with TC, PET imaging was performed at day 5 and day 6 of presentation with N13 ammonia as perfusion tracer and FDG for metabolic imaging.27

There was similar evidence of inverse perfusion/metabolism mismatch, with severe metabolic impairment at the apex, but preserved perfusion. At 3 months of follow up, the LV systolic function had normalized, with normal F-18 FDG uptake at the apex.
apex, indicating normal apical myocardial metabolism. Similarly, in the acute phase of TC, there was a reduction of MBF in all apical segments, which improved markedly on repeat PET imaging at 3 months. Cardiac MRI during the acute phase showed no evidence of delayed enhancement or myocardial necrosis. This case report using PET perfusion and metabolic imaging along with CMR demonstrated the transient and reversible severe impairment of myocardial metabolism at the apex, along with decreased MBF at the apex, likely due to microcirculatory impairment causing ischemia and myocardial stunning, without evidence of necrosis on CMR.27

Non invasive methods – CMR

CMR with pharmacological stress agents and gadolinium as the flow tracer, though not currently easily available due to financial and time constraints, can be a reliable noninvasive method of detecting CMVD. It can detect segmental and global perfusion defects, and regional and global CBF.10 In a large multicenter prospective study involving 7 tertiary centers in Europe and North America, Eitel et al evaluated 256 patients of TC with cardiac MRI at initial presentation, and at 1 and 6 month follow-up.28 CMR provides important information on reversible (inflammation, ischemic edema), and irreversible (fibrosis/necrosis) myocardial injury. Out of 256 patients, 93% (239 patients) underwent MRI at a median of 3 days after presentation, and in the 34% patients who did not receive follow up MRI at 1 & 6 months, echo was used to document complete recovery of LV function. Myocardial edema was assessed in T2 weighted images by the ratio of SI (signal intensity) in myocardium compared to that of skeletal muscle. Early gadolinium enhancement (EGE) was used as a maker of hyperemia and capillary leakage. Myocardial inflammation was considered to be present if at least 2 out of following 3 criteria were present: T2 SI ratio of 1.9 or greater, EGE ratio of 4 and above, and non-ischemic fibrosis, consistent with the Lake Louise consensus criteria for CMR diagnosis of myocardial inflammation. Late gadolinium enhancement (LGE) was used to detect myocardial necrosis/ fibrosis, with SD cutoffs of >3 and >5 SD above the mean SI of apparently normal myocardium used as thresholds for indicating myocardial fibrosis. All 256 patients underwent coronary angiography, with apical ballooning pattern seen in 82% of patients, midventricular ballooning in 17% of patients and basal inverted ballooning pattern seen in 1%. MRI cine images confirmed the ballooning patterns, and 34% of patients had biventricular ballooning. CMR also confirmed moderate to severe LV dysfunction in all patients. MRI revealed myocardial edema in 81% of patients in a characteristic transmural midventricular to apical pattern corresponding to the areas of LV dysfunction. Patchy or focal LGE was seen in 9% of patients using a threshold of 3 SD rather than 5 SD above mean of normal remote myocardium, however the SI difference was lower than that typically seen in acute myocardial infarction, with patients with focal LGE having higher troponin levels than those without LGE. (0.6, IQR 0.3-1.7 vs. 0.4, IQR 0.10-1.0 ng/m, p=0.02). Out of the total, 164 patients underwent all components required for Lake Louise criteria for CMR diagnosis of inflammation, including T2 SI ratio, EGE and LGE and 67% were positive for myocardial inflammation in the acute phase (elevated T2 SI ratio and EGE). Subsequent follow up MRI (at median of 97 days after initial presentation, performed in 158 patients) and/or echo showed normalization of LV function and significant decrease in end systolic and end diastolic volumes and T2 SI ratios and EGE. None of the patients had LGE >5 SD above mean. Myocardial inflammation, edema and absence of fibrosis could thus typify the findings in TC patients. Thus, the pathophysiology of TC likely involves myocardial edema and inflammation which are markers of reversible myocardial injury, and the absence of LGE alludes to lack of irreversible myocardial necrosis in this disease. The authors contend that LV dysfunction in a noncoronary distribution pattern, myocardial edema corresponding to areas of LV dysfunction, with a T2 SI ratio >1.9, an EGE ratio of >4, and absence of significant LGE (>5 SD), with complete or near complete resolution of these findings in a few weeks, can be used to assist the CMR diagnosis of TC. 28 Although the absence of LGE is usually expected in most cases of TC and is a common diagnostic criterion in most CMR imaging centers, it is to be remembered that up to 10% of TC patients may demonstrate focal or patchy (not necessarily apical) subendocardial LGE which is usually within 3 SD above the mean. The likely pathogenetic factors playing a role in subendocardial LGE in TC include myocardial inflammation, increased LV wall stress, or transient ischemia and microcirculatory disturbances/ dysfunction.29 High intraventricular pressure may also precipitate perfusion abnormalities and focal myocardial ischemia, even in the absence of a baseline significant epicardial coronary artery stenosis. Interestingly, the presence of focal LGE in TC if observed is usually in the acute phase which most often is not present in the late follow-up CMR suggesting a relatively benign prognosis of TC and non-persisting effect on the global LV function, which is in contrast to the LGE patterns observed in myocardial infarction or myocarditis.30

Non invasive methods- SPECT MPI

In a study by Abe et al, 2003 described previously, 13 patients with TC underwent resting Tc-99m tetrofosmin SPECT tomographic imaging during the acute phase.4 Significantly reduced Tc-99m tetrofosmin in the left ventricular apex was seen in 11 patients (85%). End diastolic images also showed decreased tracer uptake at the apex. Repeat imaging showed return of normal perfusion at the apex in all 11 patients 25-90 days after presentation.4 Given lack of epicardial perfusion abnormality on coronary angiography, the cause of the scintigraphic abnormalities were thought to be due to mitochondrial abnormalities, given subcellular localization of radiotracer in myocardial cells after active uptake. Furthermore, given scintigraphic abnormalities at the apex at end diastole, a partial volume effect was considered unlikely.5

Role of inflammation in TC pathogenesis

In patients without epicardial obstruction, lower CFR levels are a marker of microvascular dysfunction, and elevated levels of CRP have shown to correlate with lower CFR levels.31 Cases of acute pericarditis complicated by TC have also been reported.31 There have been other reports of pericarditis associated with TC, with pericarditis occurring either preceding onset of TC or in the resolution phase of TC.32 An interesting case of lupus myopericarditis precipitating development of TC has also been described.33 In cases with TC as the primary pathology, myocarditis with resulting adjacent involvement of pericardium can lead to pericarditis. In patients with preceding myopericarditis, myopericardial inflammation resulting in intense chest pain and sympathetic stimulation may result in neurogenic stunned myocardium and trigger development of TC.31,32 CMR can have an almost 80% diagnostic accuracy in detecting myocardial inflammation in TC patients.33 In a study by Eitel et al, 67% of TC patients’ demonstrated evidence of myocardial inflammation on T2 weighted images.26 Myocardial edema was seen in 81% of patients with patchy delayed gadolinium enhancement seen in 9% of TC patients. In another study by the same author, 62% of patients had elevated inflammatory markers such as elevated edema ratio on
T2 weighted images, and elevated global reactive enhancement (GRE) on pre and post contrast T1 weighted CMR imaging and also had concomitant pericardial effusion, all indicative of acute inflammatory process. Recent studies including a large metaanalysis have noted that the prevalence of diabetes mellitus in TC patients is much lower than other traditional cardiac factors (such as hypertension, smoking) and is estimated to be around 10-17%. In another small study by Khalid et al, the prevalence of diabetes mellitus was 6.25%, in only one out of 16 patients. An intriguing plausible explanation is autonomic nervous dysfunction and therefore blunted response to catecholaminergic surge and/or decreased catecholamine secretion in diabetic patients making them less susceptible to TC triggered by stressful stimuli. Sympathetic blockade as an effective therapeutic strategy and sympathectomy in animal models preventing cardiac dysfunction also lends credence to this hypothesis.

Conclusion

Although there is some conflicting evidence, the preponderance of studies thus far, both invasive and noninvasive, strongly imply a major role of microvascular dysfunction in the pathogenesis of TC. Invasive studies (using TIMI frame counts, myocardial perfusion grading, intracoronary Doppler evaluation of vasomotor function, coronary flow reserve and thermolodiation method to assess index of microvascular resistance) and noninvasive studies (using doppler echocardiography, myocardial contrast echocardiography, SPECT/PET metabolism/perfusion and Cardiac MRI) have all demonstrated coronary microvascular dysfunction in the acute phase of takotsubo cardiomyopathy.

Of significance, all of these microvascular abnormalities demonstrated by both invasive and noninvasive testing usually are transient and reversible, with follow up testing indicating normalization of microvascular function, in parallel with recovery of LV function. The precise mechanism of this transient coronary microvascular dysfunction, although not completely understood, could involve adrenoreceptor overstimulation/sympathetic hyperactivity, resulting from a catecholamine surge secondary to physical or emotional stress and differences in the type and density of adrenoreceptors in the cardiac apex versus the base might partly explain the proclivity of transient apical dysfunction in TC. Regional wall motion abnormalities in TC seem to recover subsequent to recovery of microcirculatory dysfunction, therefore suggesting that resolution of transient microvascular circulatory dysfunction is essential to recovery of wall motion dysfunction. Patients with TC may also have subclinical microvascular dysfunction persisting over time, or conversely, subclinical microvascular abnormalities with endothelial dysfunction may cause a predisposition to development of TC, in post-menopausal women, with lack of estrogen perhaps contributing to endothelial dysfunction. Although the precise mechanism of TC pathogenesis is not conclusively established, the weight of evidence suggests that microvascular dysfunction likely remains one of the important contributing factors towards the pathogenesis of this disorder. Therapeutic approaches targeting coronary microvascular function to potentially hasten recovery from TC or to ameliorate chances of recurrence must be further explored.

Declarations of Interest

The authors declare no conflicts of interest.

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