Mechanisms of Takotsubo Cardiomyopathy; Role of Microcirculatory Dysfunction

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Abstract

Takotsubo cardiomyopathy is characterized by reversible left ventricular dysfunction, typically preceded by an emotional or a physical stressor. The underlying pathophysiologic mechanisms include multivessel coronary vascular spasm, microvascular dysfunction, neurogenic stunning of the myocardium and catecholamine surge. Microcirculatory dysfunction may play a key role in the evolution of this syndrome especially in the acute phases of the illness. Severe invasive and noninvasive modalities are utilized to ascertain any compromise in coronary perfusion in Takotsubo cardiomyopathy, including Doppler guidewire technique, Thrombolysis in myocadial infarction (TIMI) frame count (TFC), TIMI myocardial perfusion grade (TMPG) and nuclear imaging techniques. TIMI frame count can be utilized as a diagnostic marker and clinical indicator in assessment of microvascular function or coronary flow in patients with Takotsubo cardiomyopathy.

Keywords: Takotsubo cardiomyopathy; Microvascular dysfunction; TIMI frame count; Coronary flow reserve; Microcirculatory disorder

Citation: Khalid N, Aftab Ahmad S, Umer A. Mechanisms of Takotsubo Cardiomyopathy; Role of Microcirculatory Dysfunction. International Cardiovascular Forum Journal. 2016;5:30-32. DOI: 10.17987/icfj.v5i0.237

Introduction

Since its first description in Japan in the 1990s, Takotsubo cardiomyopathy (TCM) has garnered significant scientific interest and media attention. We have seen a dramatic increase in research on the subject in the past two decades which has led to somewhat improved understanding of the disease process. Various pathophysiologic mechanisms have been proposed for its development: these include multivessel epicardial coronary artery spasm, catecholamine spillover with resultant cardiotoxicity, neurogenic stunned myocardium but the true cause of TCM still remains elusive. Another causative factor that has been described in recent literature is the microcirculatory or endothelial dysfunction or coronary slow flow (CSF) especially in the acute phase of the illness.¹⁻⁹ It has been suggested that the neurogenic stunning of the myocardium or catecholamine spillover (which are central to the syndrome’s etiology) may lead to impairment of microcirculation. Alternatively, it has also been postulated that these coronary flow abnormalities may be present before the acute episode in susceptible individuals. Whether these disturbances represent a preceding event or sequelae of the catecholaminergic storm raises an important cause vs. consequence question. It is certainly possible that in a small subset of these patients, coronary slow flow may be a related bystander phenomenon; nevertheless, it still remains a strong contender for the causative pathophysiology of Takotsubo cardiomyopathy.⁶⁻¹⁰

TIMI frame count a novel technique:

Takotsubo cardiomyopathy is an acute cardiac syndrome characterized by transient systolic dysfunction of the apical and/or mid segments of the left ventricle that mimics myocardial infarction but without significant obstructive coronary artery disease.¹⁻¹³ Several invasive and non-invasive modalities have been utilized to assess myocardial perfusion both during the acute and recovery phase of TCM.⁵⁻¹⁵,¹²⁻²³ These techniques include Doppler guidewire technique, Thrombolysis In Myocardial Infarction (TIMI) frame count (TFC) and TIMI myocardial perfusion grade (TMPG) calculation.⁵⁻¹⁵,¹²⁻²³ Gibson et al. introduced a novel method in 1996 called ‘TIMI frame count’ for measuring coronary flow velocity from coronary angiograms.⁵⁻¹⁵ Since then TFC has been used as a quantitative index to determine microcirculatory function in patients with acute coronary syndrome after primary coronary angioplasty as a predictor of functional recovery. Few studies have employed this method in Takotsubo cardiomyopathy as well for indirect assessment of microcirculation.⁵⁻¹⁵ TIMI frame count is defined as ‘the number of frames required for the contrast material to travel from coronary ostium to the standardized distal landmark’.⁵⁻¹⁵ TFC is a simple, objective, reproducible and inexpensive test for calculation of the coronary flow reserve. The term ‘corrected TIMI frame count’ (CTFC) is applied when a correction factor is applied to account for the contrast material to travel from coronary ostium to the standardized distal landmark.⁵⁻¹⁵

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ISSN: 2410-2636 © Barcaray Publishing
Studies favoring the role of microcirculatory dysfunction in Takotsubo Cardiomyopathy:

**Utilizing TIMI Frame Count:**

We recently conducted a microcirculatory analysis in a retrospective cohort of sixteen patients with Takotsubo cardiomyopathy by computing TIMI frame counts in the three main coronary arteries (the LAD, CX and RCA) and compared it with age matched controls (n=15).6,7 Our results showed that the mean corrected TFC values were elevated by a total of three frames (reaching statistical significance) in the LAD of patients with Takotsubo cardiomyopathy compared with LAD of control individuals, with no difference observed between the two groups in other vessels.6,7 The exact reason for this selective distribution of microvascular dysfunction in the left anterior descending artery territory is unclear although it may explain the predisposition for apical involvement in Takotsubo cardiomyopathy patients.6,8

At least three studies have been previously performed which show a similar correlation between abnormal TIMI frame count and microvascular dysfunction.14-16 Bybee et al. noted abnormal TIMI frame counts during acute phase of Takotsubo cardiomyopathy in sixteen patients in all three coronary vessels suggesting that diffuse impairment of coronary microcirculatory function may play a role in underlying pathogenesis although it remained unclear if microvascular dysfunction was the primary cause or a secondary phenomenon.14 Similarly Kurisu et al. found significantly higher TFCs in 28 patients with TCM when compared with controls both during the acute phase and follow-up.15 Fazio et al. also noted abnormalities in all three vessels in their cohort of 24 patients suggesting a pathological slowdown of the general coronary flow.16

**Utilizing other modalities:**

We found at least four studies and one case report in literature utilizing techniques other than TIMI frame count that support the presence of microvascular dysfunction in Takotsubo cardiomyopathy.17-21 Kume et al. recorded coronary flow velocity spectrum and coronary flow velocity reserve (CFVR) by using Doppler guidewire technique in the acute phase and three weeks later in the three main coronary vessels along with assessment of deceleration time of diastolic velocity (DDT).17 They noted that both the CFVR and DDT decreased during the acute phase of the illness with normalization noted at three weeks.17 These findings suggested that microvascular dysfunction may play a role in the acute phase of Takotsubo cardiomyopathy.17

Yoshida et al. described coronary perfusion abnormalities and severe myocardial metabolic disturbances in patients with Takotsubo cardiomyopathy based on the results of thallium-201 myocardial single-photon emission computed tomography (SPECT) and F-18 fluorodeoxyglucose myocardial positron emission tomography (FDG PET).18 They noticed markedly decreased uptake at the apical region on F-18 FDG PET images whereas thallium 201 images showed only mildly reduced uptake.18 The affinity for decreased uptake may possibly be related to increased density of beta receptors noted in apex.18 The metabolic disturbance was likely linked to the sudden preceding stress and this resulted in corresponding perfusion abnormalities.18

Elesber et al. calculated Thrombolysis In Myocardial Infarction (TIMI) myocardial perfusion grade (TMPG) via angiograms in a cohort of 42 patients.19 TMPG is an index of myocardial perfusion and was noted to be in 29 (69%) of the patients suggesting impaired microcirculation.19 Interestingly patients with abnormal TMPG had higher peak troponin levels and greater propensity to have electrocardiographic changes (ST-segment elevation or deep T-wave inversion) compared with patients with normal TMPG.19 These findings suggested that the disturbed myocardial perfusion correlated with the degree of myocardial injury.19

Ito et al. assessed myocardial perfusion via 99mTc-tetrofosmin myocardial SPECT in the acute, subacute and chronic phases of Takotsubo cardiomyopathy.20 They noticed that the myocardial perfusion scores were impaired at admission and showed improvement in the subacute and chronic phases of TCM. They supported their findings with nuclear imaging findings of diminished myocardial perfusion in the absence of obstructive coronary artery disease.20 Similarly, Nishikawa et al. employed (99m) Tc-tetrofosmin myocardial single photon emission computed tomography (SPECT) showed severely decreased uptake in the apex.21 Additionally they noticed that coronary flow reserve measured with a Doppler guide wire was also severely reduced. The reduced apical uptake, and the reduced coronary flow reserve returned to normal over two weeks and one month respectively.21 These studies suggest that microvascular dysfunction plays a key role in the development of Takotsubo cardiomyopathy.

Studies not favoring the role of microcirculatory dysfunction in Takotsubo Cardiomyopathy:

In contrast, some other studies suggest a limited role of microvascular dysfunction in Takotsubo cardiomyopathy.22-24 Sharkey et al. evaluated 59 patients (all women aged 32–90 years) with Takotsubo cardiomyopathy and noted that patients with or without ST-segment elevation didn’t differ with regard to clinical outcome, ejection fraction, abnormal left ventricular contraction patterns (including the apical sparing variant) or TFC.22 Abe et al. investigated 17 patients utilizing Technetium-99m tetrofosmin tomographic imaging and noted decreased uptake at the left ventricular apical region in 11 patients (85%) that later returned to normalcy.23 No significant stenosis or angiographic slow flow in epicardial coronary arteries was observed. Furthermore, no significant abnormality in the coronary microcirculation was detected by Doppler guidewire technique.23 In summary, there is some evidence (albeit limited) that does not support the role of microcirculation in etiopathogenesis of TCM, however given the smaller sample size, limited data many clinicians still support the microcirculatory disorder hypothesis as one of the contributors towards Takotsubo cardiomyopathy.

**Conclusion**

Taken together, these studies suggest that coronary microcirculatory abnormalities may play a key role in the evolution of Takotsubo cardiomyopathy. Various invasive and non-invasive techniques support the presence of disturbances in microcirculation especially in the acute phase of Takotsubo cardiomyopathy. However, the association may not indicate a cause and effect relationship. TIMI frame count can be utilized as a diagnostic marker and clinical indicator in assessment of microvascular function or coronary flow in patients with Takotsubo cardiomyopathy.

**Declarations of Interest**

The authors declare no conflicts of interest.

**Acknowledgements**

The authors state that they abide by the “Requirements for Ethical Publishing in Biomedical Journals”.24
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