Time-Related Microcirculatory Dysfunction in Patients With Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM) has been described as an acute reversible heart failure syndrome resulting from a transient contractile dysfunction of a large region of the left ventricular myocardium in the absence of epicardial coronary obstruction or plaque rupture. In these patients, acute microvascular impairment has been previously demonstrated at the time of clinical presentation by measuring the index of microvascular resistance (IMR). In the present study, we sought to prospectively assess the presence of microcirculatory dysfunction by invasively measuring the IMR in patients presenting with TCM. Specifically, we sought to elucidate whether a time-dependent trend in microvascular damage resolution exists.

Methods | During a 6-month period, 15 consecutive patients with high diagnostic suspicion of TCM were prospectively included in our study. Initial inclusion criteria were defined as the presence of symptoms and regional wall motion abnormality and/or ballooning compatible with TCM and the absence of significant coronary stenosis. Diagnoses relied on the Mayo Clinic diagnostic criteria, including clinical presentation, electrocardiogram and troponin level changes, a characteristic morphology at the left ventricular angiogram, and absence of significant lesions on coronary angiography. Eventually, 1 patient was excluded because of the presence of myocarditis criteria on magnetic resonance imaging. The Hospital de la Princesa Ethics Committee approved the protocol, and each patient provided written informed consent.

After angiography, invasive physiological assessment of the microcirculation was systematically obtained in every patient. A pressure wire (Certus; St Jude Medical) was advanced until the wire sensor was located in the left anterior descending artery, with the transducer distance at 7 to 10 cm from the guide tip. Intravenous adenosine (140 μg/kg/min) was administered to induce steady-state maximal hyperemia. When a hyperemic state was reached, three 1-mL injections of room-temperature saline were given. The IMR was calculated as the ratio between distal coronary pressure at maximal hyperemia and the inverse of hyperemic mean transit time. According to previous studies, the upper normal limit of the IMR was set at 22. The IMR temporal correlation was analyzed using the Spearman test.

Results | All 14 patients were women with a mean (SD) age of 74 (13) years. The most common trigger of TCM was emotional stress (6 [42.9%]). A typical apical TCM ventricular morphology was identified in 11 patients (78.6%). The most frequent electrocardiographic change was T-wave inversion in precordial leads, which was present in 11 patients (78.6%). Most patients (9 [64.3%]) presented with a Killip class I, and 1 patient was in cardiogenic shock. Angiographic mean (SD) left ventricular ejection fraction was 41% (9%). Coronary angiography revealed no significant epicardial coronary lesions in any patient. The median (interquartile range) time from symptom onset to the IMR measurement was 25 (7-60) hours. The median (interquartile range) left ventricular end-diastolic pressure was 16 (8-24) mm Hg, and the median (interquartile range) coronary flow reserve was 1.4 (1.0-2.7). All patients had microvascular dysfunction (ie, an IMR greater than 22) with a mean (SD) IMR of 53 (22). Importantly, a significant negative linear correlation was observed between the extent of microvascular dysfunction and the time from symptom onset to the IMR measurement ($R$, −0.72; $P = .03$) (Figure).

Discussion | The mechanism of reversible microvascular dysfunction still remains unknown but appears to differ from that seen in ischemic heart disease. As cardiac microcirculation is directly innervated by the brain stem that induces vasoconstriction, it is tempting to speculate that microvascular injury might have a direct neurogenic etiology in this entity. However, our findings suggesting a time-related recovery of microvascular dysfunction cannot establish causality. Further research should provide novel insights on the role of microvascular dysfunction of patients with TCM.

Conclusions | Our study confirms the presence of microvascular dysfunction in a prospective cohort of consecutive patients with TCM. Moreover, our findings suggest that microvascular injury plays a role in the pathophysiology of TCM.

Figure. Time-Related Evolution of Microvascular Dysfunction in Takotsubo Myocardopathy

Time represents the time since symptom onset to index of microvascular resistance (IMR) measurement. The solid line indicates the regression line; the dotted line, the prespecified IMR threshold; the points, each individual IMR measurement.
Indeed, microvascular damage with temporal evolution toward resolution might closely correlate with myocardial stunning recovery.

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Recovery in Patients With Dilated Cardiomyopathy With Loss-of-Function Mutations in the Titin Gene

A high proportion of dilated cardiomyopathy (DCM) cases arise from loss-of-function mutations in the titin gene (TTN), which codes for the sarcomeric protein Titin. Although TTN plays a fundamental role in maintaining cardiac contractility, it has recently been demonstrated that individuals with TTN mutations recover systolic function with left ventricular assist device support (in addition to standard medical therapy). However, to our knowledge, it remains unknown whether standard medical therapy for systolic dysfunction is equally effective in these patients without left ventricular assist device support. Our objective was to compare the prevalence of TTN mutations in patients with DCM receiving standard pharmacological therapy with and without recovery of systolic function.

Methods | We recruited 141 patients with DCM referred to the Heart Failure Clinic of the McGill University Health Centre in Montreal, Quebec, Canada, an academic tertiary care heart failure clinic providing heart transplant and mechanical circulatory support, for medical therapy between April 2010 and January 2012 (mean [SD] age, 53.6 [11.9] years; range, 18-81 years). Dilated cardiomyopathy was defined as having a left ventricular ejection fraction of 45% or less. Patients with an ischemic etiology or other obvious structural abnormality (eg, congenital heart disease or noncompaction syndromes) were excluded. Recovery was defined as a left ventricular ejection fraction greater than 50% at follow-up after 1 or more years. Clinical characteristics of those who recovered are shown in the Table. All coding exons of TTN were sequenced using the MiSeq Reagent Kit version 2 (Illumina) after targeted capture using the Access Array system (Fluidigm). Sequence data were analyzed with the Genome Analysis Toolkit (Broad Institute) and Variant Effect Predictor (Ensembl), and variants were compared with the Exome Sequencing Aggregation Consortium database (http://exac.broadinstitute.org). The McGill University Health Centre Biomedical Research Ethics Board approved the protocol, and all participants provided written informed consent. Comparisons were performed using Fisher exact test, Student t test, or the Mann-Whitney test. Statistical significance was defined as P < .05. The median read depth of exonic base pairs was 421X, with 99.3% of identified variants having a read depth greater than 15X.

Results | After excluding variants found in the 1-band and those at greater than 0.0001 minor allele frequency in the Exome Sequencing Aggregation Consortium database, 26 TTN truncating variants were identified in the 128 successfully sequenced samples from our DCM cohort. All of these variants were heterozygous mutations causing truncation in the 2 TTN cardiac isoforms, N2BA and N2B. Thus, all 26 were considered to be pathogenic for DCM and represented 26 of 128 patients (20.3%) of our sample. Patients with recovery of systolic function with medical therapy were equally likely to have TTN mutations compared with those without recovery (14.3% vs 22.0%; P = .44) (Table).

Discussion | We demonstrate that truncating TTN mutations are frequently observed in patients with DCM who recover systolic function with standard medical therapy alone. Our results suggest that despite the key role played by TTN in cardiac function, individuals with these mutations can recover systolic function and are equally likely to experience recovery as those with other causes of DCM. While it was recently shown that recovery is possible in patients with DCM who have a truncating mutation in TTN with mechanical unloading therapy support, our findings that recovery is possible in those receiving medical therapy alone is consistent with another recently published study. However, not all patients with TTN mutations receiving medical therapy recovered. While the specific mutations that cause DCM and their penetrance are...