Under the hood of the stunned takotsubo heart

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Takotsubo or stress-induced cardiomyopathy is a syndrome of transient acute regional left ventricular (LV) systolic dysfunction beyond a single epicardial vascular distribution, predominantly involving the mid-cavity and apex, that mimics an acute myocardial infarction with new ST-segment elevation or T wave inversion, but without angiographic obstructive coronary artery disease or acute plaque rupture or other causes of similar LV wall motion abnormalities (e.g., pheochromocytoma, myocarditis, etc.).[1,2,3] Less common variants have been described including the mid or basal or focal or global types depending on the site of LV wall motion abnormalities.[4,5] A physical or emotional trigger is often but not always present. The unique ''short neck round-flask'' appearance of the apical LV ballooning during end systole resembles its 'namesake' the takotsubo (Japanese octopus fishing pot or trap).[2] This entity is much more common in women and older adults, and when compared to acute coronary syndromes, takotsubo cardiomyopathy (TC) patients also have higher rates of neurologic or psychiatric disorders.[4]

The pathogenesis of myocardial stunning in TC is not well understood. Catecholamine triggered myocyte injury, coronary artery spasm, and/or microvascular dysfunction-mediated stunning have been postulated,[2,6,7] as is dynamic mid-cavity or LV outflow tract obstruction from increased adrenergic tone.[8,9] Role of the brain–heart axis in this disease has also been described.[10] Christensen and colleagues noted decreased late heart/mediastinal ratio and increased ^{123}I-mIBG wash out ratios as well as increased levels of plasma catecholamines in 32 patients in the subacute state of TC, supporting a role of adrenergic hyperactivity.[11] Wittstein and colleagues demonstrated markedly higher plasma catecholamine levels at presentation in 13 patients with stress-induced cardiomyopathy compared to 7 patients with Killip class III acute myocardial infarction.[6] Of the 5 TC patients who underwent endomyocardial biopsy, 4 had interstitial infiltrates consisting primarily of mononuclear lymphocytes and macrophages and contraction bands without myocyte necrosis. The fifth patient had an extensive inflammatory lymphocytic infiltrate and multiple foci of contraction band myocyte necrosis.[6]

Relative to perfusion, the reduced ^{123}I-beta-methyiodophenyl pentadecanoic acid uptake in the non-infarcted apical myocardium of TC patients from impaired fatty acid metabolism may in part reflect transient ischemic damage or stunned myocardium from catecholamine surge or microvascular spasm (ischemic memory).[12] Vasospasm of the epicardial coronary arteries is generally considered an unlikely sole mechanism as the regional wall motion abnormalities do not correspond to the perfusion territory of a single coronary artery, and only a few patients have shown spontaneous or provocative multivessel epicardial spasm.[9,13] However, using intracoronary acetycholine testing, Angelini provides evidence in favor of multivessel coronary artery spasm from endothelial dysfunction as the causative mechanism of apical LV ballooning in 4 patients and mid-ventricular ballooning in 1 patient.[14,15] Using myocardial contrast echocardiography at baseline, during adenosine infusion and at 1-month follow-up, Galiuto and associates demonstrate reversible coronary microvascular dysfunction as the probable pathogenic mechanism in 15 patients with TC.[16] Naegele and colleagues highlight the relevance of endothelial dysfunction in 22 patients with TC compared to 21 matched controls, even in the stable phase of the disease. A trend of higher basal sympathetic nervous activity was

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also noted in a subgroup of 12 patients.[17] The regional distribution of myocardial stunning in response to high circulating catecholamine levels has been explained by the higher density of β-adrenoreceptors in the LV apex of the mammalian heart.[18,19]

Variations in myocardial perfusion and metabolism described in animal models of repetitive myocardial stunning provide insights into the perfusion and metabolism imaging patterns observed in TC patients. In a canine model, Di Carli and colleagues showed prolonged but reversible reduction in LV systolic function that was associated with a significant downregulation of glucose and oxidative metabolism despite restoration of normal myocardial blood flow (i.e., decreased metabolism with near normal perfusion). In images obtained 3-4 hours and 1 day after reperfusion, blood flow was near normal in stunned regions, however, with reduced glucose uptake relative to normal myocardium that normalized 1 week after reperfusion.[20] On the other hand, in a porcine model, McFalls and colleagues observed a sustained increase in myocardial FDG uptake relative to perfusion (i.e., increased metabolism with reduced perfusion) 24 hours following ischemia that was inversely proportional to the severity of LV dysfunction. The LV function, perfusion and metabolism returned to normal by 7 days.[21] The enhanced myocardial glucose metabolism post reperfusion was ascribed to glycogen repletion, lactate production, and nonoxidative glycolysis.[22] The divergent myocardial glucose uptake patterns as noted above, i.e., reduced in the canine model and increased in the porcine model, were attributed to differences in experimental design prior to ^{18}F-FDG injection (i.e., hyperinsulinemic-euglycemic clamping in the Di Carli study vs IV dextrose loading in the McFalls group).[20] Maki and colleagues also observed that the differential increase in FDG uptake in the ischemic vs normal myocardium in the fasting state could not be reproduced during hyperinsulinemic-euglycemic clamping in the same patients with chronically occluded CAD.[23] In a rodent model of reversible 20-minute LAD coronary occlusion and anterolateral LV stunning, McNulty and colleagues demonstrated an exponential relationship between the observed increase in ^{18}F-FDG myocardial activity and degree of ^{13}N-NH3 myocardial hypoperfusion. Myocardial glucose avidity was greatest in sections with the greatest reductions in reperfusion blood flow.[24] At 24 hours, the investigators noted normal LV function of the reperfused regions with persistent reductions in myocardial blood flow, glycogen depletion, and increase in the relative utilization of circulating glucose as a glycolytic substrate.[24]

Similar to repetitive myocardial stunning, a spectrum of myocardial perfusion and metabolism imaging patterns have also been reported in TC patients. Using ^{13}N-NH3 and hyperinsulinemic-euglycemic clamp prepped ^{18}F-FDG PET, Feola and colleagues showed reductions in both coronary flow reserve and glucose metabolism in the apical segments during the acute phase in 3 TC patients that recovered completely after 3 months.[25] During the acute phase, FDG uptake was severely reduced in the apical and mid-ventricular segments in all 3 patients, with only modest reductions in stress perfusion that normalized at rest (described as an inverse-mismatch of flow/metabolism).[25] The authors suggested a transient metabolic disorder at the cellular level from a microcirculation disturbance as the potential explanation of their findings. In a case report, Obunai et al. describe profoundly reduced ^{18}F-FDG uptake in the ballooned apical myocardium with a correspondingly smaller and less severe resting rubidium-82 perfusion abnormality in a 52-year-old female with TC who was prepped with oral glucose loading for the ^{18}F-18 FDG study, in a pattern consistent with myocardial stunning.[26] Follow-up PET images 3 months later showed marked improvement of myocardial ^{18}F-18 FDG uptake. Christensen and associates also observed matched perfusion-metabolism defects in the apical and mid-ventricular regions of the LV in 16 TC patients.[27] The FDG scans were performed after 8 hours fast followed by oral glucose loading with need for intravenous insulin in 2 patients with blood glucose >7 mmol/L. On the other hand, Michayi and colleagues noted severely reduced ^{123}I-beta-methyl-iodophenyl pentadecanoic acid uptake, mildly reduced ^{99m}Tc-sestamibi uptake, and focal FDG accumulation in the LV apex, of an 85 year-old-female with TC.[28] The authors attributed the apical hypermetabolism post prolonged fasting to inflammation.

In the present issue of the journal, Kobylecka and colleagues from the Medical University of Warsaw studied the ^{18}F-FDG cardiac uptake pattern in 18 fasting TC patients and correlated the results with ^{99m}Tc-MIBI perfusion scintigraphy and echocardiography (DOI. 10.1007/s12350-016-0775-x). In 10/18 patients, the investigators noted decreased ^{18}F-FDG uptake in the apical myocardium with preserved ^{18}F-FDG myocardial activity elsewhere. 7/10 of these patients had a mild apical perfusion defect and 3/10 had normal perfusion. The remaining eight patients demonstrated apical hypermetabolism with normal perfusion in seven patients and a minor apical perfusion defect in one patient. The authors hypothesized that the two differing perfusion/metabolism patterns are probably related to disease severity, i.e., apical hypermetabolism with normal or slightly reduced perfusion a manifestation of transient vasospasm with rapid recovery and those with relatively reduced apical ^{18}F-FDG uptake and high myocardial metabolic activity elsewhere often with reduced apical perfusion, a sequela of vasospasm with delayed recovery. Although the pathogenesis of this

disorder is incompletely understood, scientific evidence favors intense physical and/or emotional stress-induced surge in catecholamines, with underlying substrates of microvascular and possibly endothelial dysfunction as the culprits and therapeutic targets of the transient myocardial stunning. At the tissue level, there are complex, variable, and reversible impairments of myocardial perfusion, cardiomyocyte fatty acid metabolism, sympathetic innervation and glycolysis triggered by ischemic LV stunning. Based on observations made by a diverse group of investigators, I would surmise that the cardiac perfusion and metabolism imaging findings in TC are a continuum from normal to decreased perfusion and hypo to hypermetabolism, influenced by many variables. The latter include differences in timing of perfusion and ^{18}F-FDG PET imaging from symptom onset, patient preparation (fasting vs glucose loading with/without insulin) and compliance, extent and severity of microvascular dysfunction (increasing FDG uptake with worsening ischemia), aging, presence of cardiomyocyte inflammation, necrosis etc. There is clearly more to learn.

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