

Takotsubo Cardiomyopathy and Coronary Artery Disease: A Meaningful Coincidence?

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Since its initial description¹, Takotsubo cardiomyopathy has generated much debate and interest. Over the past 25 years, much progress has been made in understanding this syndrome. While the clinical presentation and characteristics have been well described and agreed upon, the etiology is a bit more of a debate. At present, the most commonly accepted theory on the pathophysiology of Takotsubo syndrome (TTS) centers on excess catecholaminergic state and enhanced sympathetic activity.^{2–4} However, there is still some thought that TTS may represent an aborted myocardial infarction or the results of plaque rupture and transient ischemia and myocardial stunning. The Mayo criteria for TTS rely on the “absence of significant obstructive coronary artery disease (CAD) or angiographic evidence of plaque rupture.”⁵ Since then, there have been multiple case series, challenging the notion that coronary artery disease necessarily excludes the diagnosis of TTS. It is now increasingly accepted that the 2 conditions are not mutually exclusive, but can exist coincidentally.

In their current single-center study, Eitel et al⁶ try to shed some light on the causal association, or lack of it, between ACS with vulnerable plaque and TTS. For the first time, they describe the optical coherence tomography (OCT) findings in a patient population with TTS. Of note, the present study reiterates a significant prevalence of atherosclerotic plaques in these patients with TTS. Previously the prevalence of CAD in patients with TTS was noted to range between 10% and 61% in prior studies.^{7,8} In a prior retrospective cohort of patients with TTS, coronary atherosclerosis was present in the majority

(61%) of patients.⁷ In addition, 29% had luminal stenosis severity greater than 50% in at least 1 epicardial vessel.⁷ The clinical characteristics of TTS were recently reviewed in the International Takotsubo Registry, a consortium of 26 centers in Europe and the United States including 1750 patients with Takotsubo cardiomyopathy.⁸ In the International Takotsubo Registry there was significant coexistence of coronary disease occurring in approximately 15% of patients.⁸

Vulnerable Plaque, TCFA, and Takotsubo Cardiomyopathy

Based on a small case series of patients with TTS assessed with intravascular ultrasound (IVUS) that demonstrated a single, ruptured, atherosclerotic plaque in the mid left anterior descending coronary artery, acute plaque rupture leading to transient ischemia/injury and stunning of the myocardium has been proposed as the pathogenic mechanism underlying TTS.^{9,10} However, a rapidly growing body of evidence clearly argues against the hypothesis of plaque rupture as the underlying cause of TTS. Small retrospective IVUS studies have systematically excluded plaque rupture.^{11,12}

The thin-cap fibrous atheroma (TCFA) is the typical finding and precursor for the majority of vulnerable lesions resulting in acute coronary syndromes.¹³ Given that the resolution of IVUS is 150 to 200 μm , it is incapable of identifying the fibrous cap thickness component of TCFA (ie, $<65 \mu\text{m}$). Using IVUS-VH, TCFA are defined by a focal, necrotic core containing plaque ($\geq 10\%$ of the total plaque area) in direct contact with the lumen, and in the presence of a percent atheroma volume $\geq 40\%$.¹⁴ The accuracy of IVUS-VH to identify “necrotic core” has come into question. Intracoronary OCT has superior resolution (10–20 μm), compared to IVUS, and therefore is ideally suited to identify thin caps of TCFA that allow the identification of vulnerable plaque.¹⁵ By comparison to histopathologic data as the “gold standard,” the accuracy of OCT for characterizing plaque type was high with a sensitivity of 90% to 94% and specificity of 90% to 92% for detecting lipid-rich plaques.¹⁵ However, OCT also has its limitations. OCT is unable to give us vessel dimensions, plaque area, or “necrotic core” area, because of limited penetration of the light beams into the vessel wall.

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This is the first study demonstrating the lack of plaque rupture in the left anterior descending coronary artery confirmed by intracoronary OCT in TTS. Interestingly, >25% of patients were noted to have TCFA. Before we assume the presence of a TCFA is the “smoking gun,” we must remember that TCFA as well as ruptured plaques have also been seen in patients with stable angina and even in asymptomatic patients.¹⁶ Furthermore, there were no markers of acute plaque rupture such as intracoronary thrombi. The results of the present study using OCT strongly support those of the earlier-conducted IVUS study. Therefore, while TTS can occur in the presence of CAD, the CAD is rarely obstructive and while nearly a quarter of cases do demonstrate some vulnerable plaque, as defined by TCFA, these lesions do not show evidence of recent plaque rupture.

Cardiac MR and Takotsubo Cardiomyopathy

Another important contribution of the authors' current study is that most of their patients (69.6%) also underwent cardiac magnetic resonance imaging (CMR). The authors had previously reported on the CMR findings in TTS.¹⁷ CMR remains important to rule out other causes on the differential¹⁸ and can help distinguish TTS from other cardiac diseases.¹⁷ In their current series, 2/25 cases, nearly 10%, were excluded because of subsequent CMR findings consistent with a myocardial infarction as well as 1 case of myocarditis. Therefore, CMR helps confirm the diagnosis of TTS, by excluding other masquerading etiologies, such as myocardial infarction and myocarditis. During the acute phase of TTS, T2-weighted CMR shows edema of the left ventricular (LV) myocardium as high signal intensity, with a diffuse or transmural distribution consistent with the wall motion abnormality. These features help distinguish TTS from myocarditis and acute myocardial infarction. Late gadolinium enhancement is usually absent in TTS and its absence is an important distinguishing feature from myocardial infarction.¹⁷ Atypical cases with small areas of persistent apical transmural late gadolinium enhancement have been reported, and the authors previously described that focal or patchy late gadolinium enhancement was detected in 9% of patients. However, no late gadolinium enhancement was observed in all subjects in the present study. If available, CMR may be helpful and can be considered in suspected TTS in the acute phase. CMR may also be useful to confirm recovery of ventricular function on follow-up and to exclude myocardial infarction or other conditions such as myocarditis, which may mimic TTS.

Refining the Criteria for Takotsubo Cardiomyopathy

Since the first set of criteria (Mayo criteria) was proposed by Bybee et al⁵ over 10 years ago, we have come to understand

TTS better. Indeed, a new set of 7 diagnostic criteria was proposed earlier this year by the task force on TTS of the Heart Failure Association of the European Society of Cardiology.¹⁹ The 7 diagnostic criteria include the following:

1. Transient regional wall motion abnormalities of LV or RV myocardium that are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually extend beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease including acute plaque rupture, thrombus formation, and coronary dissection or other pathological conditions to explain the pattern of temporary LV dysfunction observed (eg, hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography abnormalities (ST-segment elevation, ST depression, left bundle branch block, T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).
5. Significantly elevated serum brain natriuretic peptide or N-terminal pro-brain natriuretic peptide during the acute phase.
6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (ie, disparity between the troponin level and the amount of dysfunctional myocardium present).
7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3–6 months).

Simply put, the current criteria state that if CAD is present, it does not contribute to the pathophysiologic state and transient LV dysfunction associated with TTS. Incorporating the additional knowledge currently provided by OCT imaging and CMR may help further distinguish TTS from other differentials. OCT can be further used to characterize CAD, if present, and eliminate the possibility of an acute plaque rupture and the culprit lesion. Furthermore, expanding on criterion number 7, recovery of ventricular systolic function on cardiac imaging may also conceivably necessitate the absence of scar or late gadolinium enhancement by CMR. So, as we learn more about TTS, our diagnostic criteria will need to continue to evolve.

Back to the Beginning

Perhaps the lone remaining question that this study does not answer is what about the possibility of vasospasm provoking a transient ischemia/injury pattern with myocardial stunning? Indeed, the first case series described by Sato et al¹ described diffuse multivessel coronary spasm provoking the

Takotsubo apical ballooning phenotype. While the authors did not comment on any observed vasospasm, and suggest that coronary vasospasm is an unlikely contributor, it cannot be excluded completely. Indeed, even nonobstructive coronary disease is associated with endothelial dysfunction and risk of spasm. Furthermore, there have been various case reports and series demonstrating coronary vasospasm in cases of presumed TTS, and provocative vasospasm has been documented in as high as 21% of patients diagnosed with TTS in 1 series.²⁰

Coincidence, or cause-and-effect? In the presence of CAD how can one reliably distinguish between TTS versus a recent ACS with transient LV dysfunction and stunning? In their current article, the authors suggest the combination of OCT and CMR provide an elegant pairing to provide further evidence of TTS. Intracoronary imaging with OCT can confirm the absence of ruptured plaque while CMR can exclude late gadolinium enhancement suggestive of a myocardial infarction or myocarditis. The finding of incidental CAD may be a coincidence in a patient otherwise presenting with clinical characteristics consistent with TTS, and the diagnosis of TTS should not be ruled out completely. A case-by-case decision process is necessary. When in doubt, this can be supplemented by further intracoronary imaging with OCT to exclude plaque rupture and CMR to eliminate the possibility of myocardial infarction.

Disclosures

None.

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