



## Images in Cardiology

# Convalescent Takotsubo Syndrome and Absolute Coronary Flow During Acetylcholine-Provoked Coronary Vasospasm

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Broken heart syndrome, also known as stress cardiomyopathy and Takotsubo Syndrome (TTS), first described in 1990, is relatively common in postmenopausal women.<sup>1</sup> TTS is believed to be due to coronary microvascular dysfunction (CMD) and catecholamine surge.<sup>1</sup> However, epicardial vasospasm at presentation, as well as with acetylcholine provocation, is well documented.<sup>1-3</sup> An alternative view is hence emerging that TTS could have a primary epicardial vasospastic etiology.<sup>2</sup> In which case, CMD is an ephemeral epiphenomenon that also convalesces with resolution of left ventricular dysfunction. To test this hypothesis a detailed coronary physiology study with accurate flow measurement is required, as illustrated by the ensuing case.

A 57-year-old woman was involved in a train crash 1 year previously. Then she had chest pain and transient left bundle branch block without significant troponin leak. Her coronary arteries were unobstructed and her left ventricle, on angiogram, showed apical ballooning with a raised end-diastolic pressure of 25 mm Hg, consistent with TTS. Her cardiac magnetic resonance scan at 1 month found a normalized heart without left ventricular hypertrophy. However, she continues to suffer angina and breathlessness. She now has persistent left bundle branch block and her symptoms are exacerbated by the recent death of a sibling. She is not on estrogen replacement therapy. She is an ex-smoker and takes only an angiotensin-converting enzyme inhibitor.

A functional cardiac catheterization was undertaken. Her central aortic blood pressure and left ventricular end-diastolic pressure were recorded with a 4-Fr pigtail catheter. These were 130/80 mmHg and 5 mmHg respectively. The latter did not rise with handgrip excluding diastolic dysfunction. Next, a 5-Fr EBU 3.5 guide catheter (Medtronic, Inc. Minneapolis,

### Novel Teaching Points

- Acetylcholine provokes a dose-dependent epicardial vasospasm in a woman with convalescent Takotsubo Syndrome.
- Intact microvasculature with preserved endothelial function mitigates within its autoregulatory range any potential flow reduction due to epicardial vasospasm.
- Isolated reduced coronary flow reserve should be interpreted cautiously, as it could be normal if coronary resistance is low.
- Conversely, high coronary resistance could be due to elevated left ventricular filling pressure of any etiology, eg, hypertension, diabetes, myocardial infarction, etc.
- The diagnosis of coronary microvascular dysfunction should take into account both coronary resistance and left ventricular function.

MN) subselected her circumflex artery. Thus, it was studied using the continuous thermodilution technique, which is a highly reproducible method.<sup>4</sup> The following estimations were obtained: hyperemic flow, 220 mL/min and minimal resistance,  $R_{\mu}$  337 ( $< 500$ ) Wood units; and baseline flow, 126 mL/min and resting resistance,  $R$  729 Wood units. The coronary flow reserve was 1.75 (220/126) ( $> 2.5$ ), which signifies CMD if taken alone. The better known index of microvascular resistance derived from adenosine-induced hyperemia and bolus thermodilution is well correlated with  $R_{\mu}$  by a factor of 20; so it would be 17 ( $< 25$ ).<sup>5</sup> Intra-coronary acetylcholine 20 ug, 40 ug, and 80 ug boluses were given. A dose-dependent increase in epicardial vasospasm occurred with a corresponding mean distal-to-proximal pressure gradient, Pd/Pa of 0.86, 0.79, and 0.58 culminating in subtotal occlusion provoking angina but without electrocardiographic ischemia (Fig. 1).

Three observations are salient. First, she does not have CMD as she has low hyperemic and baseline resistance, suggesting a vasodilated resting state. Accordingly, her reduced coronary flow reserve is normal for her. This might be

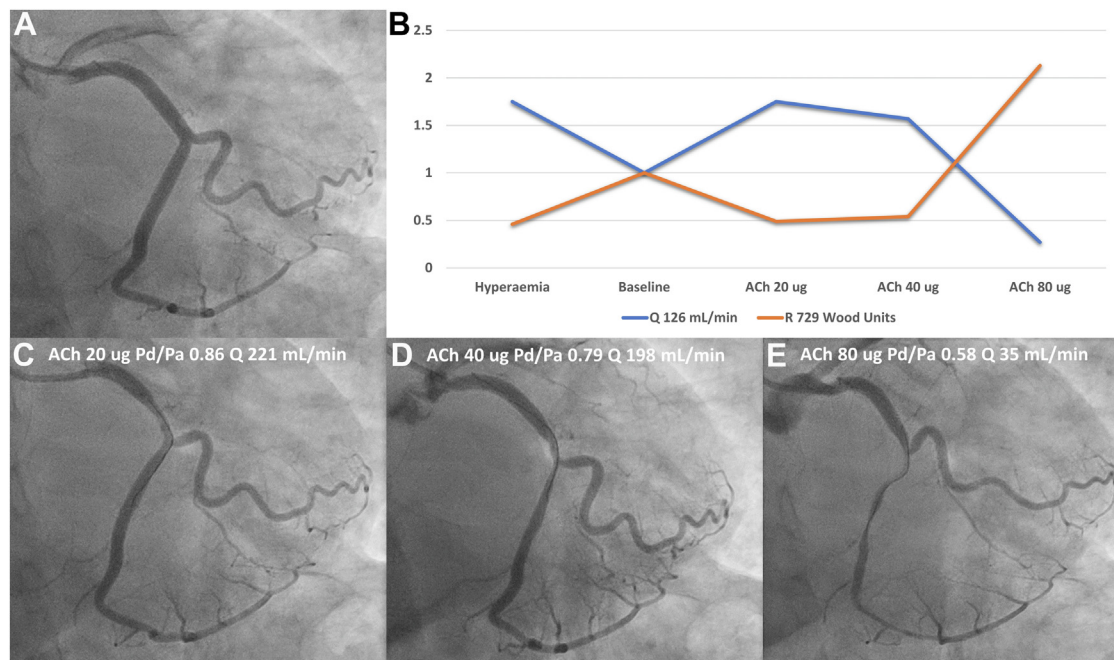
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**Ethics Statement:** Clinical management of the case reported was done with adherence to the relevant ethical guidelines. Patient informed consent was obtained prior to publication of this report.

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See page 2 for disclosure information.



**Figure 1.** (A) Unobstructed circumflex artery. (B) Baseline indices at unity with fractional changes in flow and resistance in hyperemia, and in response to acetylcholine (ACh). The low baseline absolute resistance indicates a vasodilated resting state using up part of the vasodilatory reserve. Therefore, the apparently reduced vasodilatory capacity or coronary flow reserve  $< 2.5$  is normal in this context. Further, with lower doses of ACh, although they caused epicardial vasospasm, the flow increased ( $> 1.5$ ) and resistance fell, suggesting intact microvascular endothelial function. While the severe epicardial vasospasm with high-dose ACh exceeded the microvascular autoregulatory range, causing flow to fall precipitously, precipitating angina. (C-E) Progressive epicardial vasospasm with increasing ACh doses. Ratios of mean distal-to-proximal pressure (Pd/Pa) fell as epicardial vasospasm worsened but flow rose in the first 2 doses due to preserved microvascular endothelial function, until failure of microvascular autoregulation to compensate for the severe epicardial vasospasm with high-dose ACh.

due to angiotensin-converting enzyme inhibition. Second, she has normal microvascular endothelial function because her flow increases by at least 50% with low-dose acetylcholine. Third, she has acetylcholine-induced epicardial vasospasm implying epicardial endothelial dysfunction, which could explain her continuing symptoms. In conclusion, this woman has endothelial dysfunction isolated to the epicardial vasculature, sparing the microvasculature. Consequently, epicardial vasospasm could be her TTS trigger, supporting the notion that CMD might be a secondary phenomenon. On the other hand, if CMD pre-existed, it would facilitate TTS but variants of TTS are better explained by epicardial vasospasm involving selective myocardial segments.<sup>2</sup>

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