Editorial Commentary

Takotsubo Cardiomyopathy:

Establishing Diagnosis and Causes through Prospective Testing

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The accompanying case report by Patel and colleagues[1] concerns recurrent takotsubo cardiomyopathy (TC) in the context of hyperthyroidism's onset. The authors deserve compliments on their interesting article and their correct phenotypic diagnosis of both TC and hyperthyroidism. Their report prompts me to comment about the importance of prospectively establishing the cause and nature of TC.

The medical literature's focus on clinical conditions associated with TC seems intended to clarify causative or predisposing factors in the genesis of TC. Indeed, a *simple* association of hyperthyroidism with TC might suggest that the former causes the latter; however, to convince the medical community, a prospective approach should document a *substantial* association.

Ideally, this involves duplicating the exposure to the possible cause (in this case, excessive thyroidal hormones) and carefully looking for signs of recurrent TC, usually by means of echocardiographic monitoring. The authors[1] did this in one recurrent episode. Although thyroid hormones are not known to activate any recognized mechanism that might produce TC, the second episode of TC upon the reappearance of hyperthyroidism is a significant observation arising from an implied natural experiment.

Recurrent TC is observed in fewer than 10% of cases. Its recurrence presents an opportunity to better understand the causative factors that are still at work. Two kinds of studies offer promise in this regard: 1) those that focus on reproducing TC through the administration of short-acting, suspected causative agents (typically, catecholamines in patients who develop TC after dobutamine stress testing); and 2) studies of acetylcholine (Ach) stimulation as a test of endothelial dysfunction.

Endothelial dysfunction might be an underreported predisposing condition that underlies many clinical episodes of TC.[2-4] In light of the benign, short-term, and local effects of Ach,[2-4] we and our colleagues have launched an international, multicenter investigation of its use in studying TC.[5] In pilot studies during the first few weeks after an episode of TC, Ach has frequently yielded amazingly effective results—reproducing symptoms, electrocardiographic changes, and left ventricular segmental dysfunction (at the time of severe and diffuse coronary spasm) similar to the changes that occur spontaneously during the presenting stage of TC. Then, within mere seconds, infused intracoronary nitroglycerin consistently reverses the coronary and left ventricular changes. The Ach test is correlated with the history of TC (potentially making Ach a specific diagnostic tool) and seems to predict TC recurrence (potentially making Ach an important prognostic marker). The endothelial dysfunction typically persists for only a few weeks after an episode of TC, and it responds to specific therapy involving nitrates, calcium antagonists, and possibly L-arginine.[2,3]

Like Patel and colleagues,[1] we emphasize the importance of prospective and safe mechanistic investigations in the quest to clarify the nature of TC.

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References

1. Patel K, Griffing GT, Hauptman PJ, Stolker JM. Recurrent takotsubo cardiomyopathy related to recurrent thyrotoxicosis. Tex Heart Inst J 2016;43(2):152-5.
2. Angelini P. Transient left ventricular apical ballooning: a unifying pathophysiologic theory at the edge of Prinzmetal angina. Catheter Cardiovasc Interv 2008;71(3):342-52.

3. Angelini P. Midventricular variant of transient apical ballooning: a likely demonstration of its pathophysiologic mechanism. Mayo Clin Proc 2009;84(1):92-3.
4. Angelini P. Reverse, or inverted, transient takotsubo cardiomyopathy: terms and status of an open discussion. Tex Heart Inst J 2013;40(1):60-3.
5. Tobis J. Takotsubo syndrome: a call to action. Catheter Cardiovasc Interv 2013;82(6):914.