Correspondence

Inquiries Arising From a Proposed Coronary Vasospasm–Induced Pathophysiologic Mechanism of Takotsubo Syndrome

To the Editor:

Angelini and colleagues[1] proposed that coronary vasospasm (CV) is the underlying pathophysiologic mechanism of takotsubo cardiomyopathy (TTC), which prompts the following questions and considerations:

1) Blood catecholamine levels are only modestly elevated in TTC; however, they may be much higher at the onset of TTC, after which they drop precipitously because of their short half-life.[2]
2) High-dose catecholamine administration in animal models of TTC may be justified (equivalent to pheochromocytoma-triggered TTC, characterized by massive catecholamine levels).
3) Consequent to the above, TTC and "catecholamine toxicity" precipitated by pheochromocytoma and leading to TTC are not currently considered different pathophysiologic entities, although initially the diagnosis of TTC was made after excluding pheochromocytoma.[3]
4) The low heart rate and low systolic blood pressure in some patients could be attributed to increased parasympathetic surge at the onset of TTC.[4,5]
5) Using cardiac radiation to induce endothelial dysfunction (ED) in animal models[1] before administering catecholamines is appealing and may help to elucidate the pathophysiology of TTC. What is the expected duration of induced ED, and are there other ways to induce it?
6) Does coronary artery disease–based "scaffolding" prevent CV,[1] and does the scaffolding also involve the microcirculation?
7) Might coronary calcium scores predict vulnerability to TTC?
8) How does CV induce inverse TTC (involving the base of the heart)?
9) In inverse TTC, does CV affect the intramural coronary arteries, the microcirculation of the cardiac base, or both?
10) Do patients with TTC have testable peripheral vascular ED,[6] and would it be more severe at admission than later?
11) What terminates CV in TTC?
12) Regarding direct catecholamine toxicity[1] and TTC, one could envision an abrupt, short surge of the autonomic sympathetic nervous system (ASNS) or blood catecholamines that is toxic to cardiomyocytes and leads to transient myocardial stunning.
13) Is CV the cause of TTC in young patients with inverse or neurogenic TTC?
14) Why can presumed CV in a patient with TTC manifest itself in topographically different coronary arteries as well as different myocardial territories[7] (in patients with multiple TTC episodes separated by brief periods of time) when the distribution and severity of coronary artery disease (and thus the protective effect of scaffolding) cannot be expected to be altered between different TTC episodes?
15) Should therapy for patients who have TTC include organic nitrates, nondihydropyridine calcium-channel blockers, and nitric oxide enhancers?[8]
16) Are the intramural coronary arteries more vulnerable to CV than are the epicardial arteries, because of a possible differential in their degree of ED?
17) Can autovaccination interrupt CV in TTC?
18) Should Prinzmetal angina precipitated by CV of the epicardial coronary arteries be differentiated from the vasospastic state of TTC?
19) Might TTC be due to intense ASNS-based or blood catecholamine–based intense stimulation of α_1-adrenergic receptors in the coronary vasculature, with a varying receptor ventricular topography and sensitivity?
20) Supporting the authors' assertion about the role of CV in inducing TTC is a recent case report[5] of a patient who sustained TTC in the cardiac electrophysiology laboratory while undergoing pulmonary vein ablation for paroxysmal atrial fibrillation; ST-segment elevations with gradual resolution were reminiscent of those seen in association with CV.

Insights into these points will help us to better understand the elusive, obscure character of TTC.

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Published: 5 May 2022

Conflict of interest: None

Funding/support: None

https://doi.org/10.14503/THIJ-22-7875

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