Published in final edited form as:

Heart Rhythm. 2010 December ; 7(12): 1833–1834. doi:10.1016/j.hrthm.2010.09.018.

Too Sympathetic? Role of Sympathoexcitation in Takotsubo Cardiomyopathy

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Takotsubo cardiomyopathy is classically described as a sudden and transient left ventricular apical ballooning in the absence of significant coronary artery disease. First described by Dote et al.¹, it was named Takotsubo since the narrow neck and round bottomed left ventricle resembled a traditional Japanese octopus trap. Since the initial description, patients with transient left ventricular dysfunction have been identified with both the typical apical ballooning (AB) pattern, and an alternative mid-left ventricular ballooning (MB) pattern “inverted Takotsubo”². Patients present with symptoms resembling acute myocardial infarction, including chest pain, ST segment elevation and elevated cardiac enzymes. A high proportion of patients are women who develop symptoms after episodes of high emotion (bad news or severe argument), and this disorder has captured the public’s imagination with names like “broken heart syndrome”. The interest of the medical profession has also been piqued, with almost 400 hits in PubMed for a search of “Takotsubo AND 2009”.

Despite great interest in Takotsubo cardiomyopathy, the underlying pathophysiology has remained elusive. Proposed mechanisms include coronary artery vasospasm, microcirculatory abnormalities and catecholamine-related toxicity. Coronary artery spasm was suggested as the mechanism in the initial case series¹, with transient ischemia inducing short-term myocardial stunning. Arguing against this hypothesis are that coronary spasm could be provoked in only a minority of patients³, wall motion abnormalities that do not follow a coronary artery distribution, and histological changes that are not typical seen with ischemia (including contraction band necrosis)⁴. Coronary microcirculatory abnormalities have also been reported in patients with Takotsubo cardiomyopathy. Using both Doppler flow-wire assessments⁵ and TIMI frame counts⁶, microcirculatory dysfunction was noted in multiple coronary arteries in patients with stress cardiomyopathy. It is not clear whether the microcirculatory dysfunction is the primary problem or secondary to adrenoceptor activation. Elevated catecholamine levels have been reported in patients with Takotsubo cardiomyopathy⁷. Emotional stress or other forms of physiological stress (e.g. trauma or surgery) can lead to acute elevations in sympathetic nervous system tone, and large increases in synaptic norepinephrine (the main neurotransmitter in the sympathetic nervous system). Reversible left ventricular dysfunction can also result from excessive catecholamine levels resulting from a pheochromocytoma⁸ or high exogenous doses of epinephrine⁹, pointing to an etiological role for catecholamines. Supporting this “sympathoexcitation” hypothesis, contraction band necrosis (which is characteristic of

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catecholamine induced myocyte injury) is seen on histology⁴. ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) uptake in cardiac sympathetic nerves is decreased in patients with stress cardiomyopathy, suggesting cardiac sympathetic nerve damage¹⁰.

In this issue of *Heart Rhythm*, Bonnemeier et al.¹¹ have advanced our understanding of the role of the sympathetic nervous system in 37 patients with Takotsubo cardiomyopathy, in particular in those patients with different presentations. In a subset of patients, they performed ¹²³I-MIBG cardiac scans and cardiac perfusion scans patients with the AB pattern vs. MB pattern. They found that all patients had defects on the ¹²³I-MIBG scan in the region of the wall motion abnormality, in the absence of perfusion defects. These results support the importance of sympathetic nerve damage in Takotsubo cardiomyopathy.

They also used traditional and advanced heart rate variability techniques to compare profiles in 27 AB pattern patients and 10 MB pattern patients with transient LV dysfunction to test the hypothesis that autonomic modulation might account for altered regional dysfunction. Using 24 hour Holter monitors collected on Day 3, patients with the MB pattern (compared to the AB pattern) had a higher heart rate, greater low frequency power and a greater low frequency to high frequency (LF/HF) ratio. These data are consistent with an increase in sympathetic tone affecting the sinus node in the MB patients compared to a lesser or no effect on the sinus node in the AB patients. The authors interpret these data as representing differential activation of the left stellate ganglion (and left cardiac sympathetic nerves) in patients presenting with AB and the right stellate ganglion (and right cardiac sympathetic nerves) in patient presenting with MB. Another possible explanation might be that patients with AB vs. MB have differences in adrenoceptor density accounting for different areas of damage with cardiac sympathetic overload. Arguing against this theory is the observation that some patients have had repeated episodes of Takotsubo cardiomyopathy involving different segments of the left ventricle^{12, 13}. It seems unlikely that adrenoceptor density would vary greatly within the same individual.

People who view the sympathetic nervous system as a monolithic “all or none” system might find this inference of differential activation odd. It has long been recognized that the sympathetic nervous system can activate differentially on a regional basis, and details are available in a recent excellent review on this topic¹⁴. For example, the traditional pathophysiological model of neurally mediated syncope involved a loss of sympathoneural tone and an increase in sympathoadrenal discharge around the time of faint¹⁵. Autonomic traffic can lateralize, with differential effects from right or left sided strokes or seizures^{16, 17}. Closer to the heart, left cardiac sympathetic nerves innervate the AV node and predominantly the inferoposterior portions of the left ventricle¹⁸. Unilateral denervation of the left stellate ganglion has minimal effects on the heart rate, in contrast to the increase in heart rate and arrhythmias that can result from unilateral denervation of the right stellate ganglion¹⁸.

Many questions remain unanswered about the role of sympathoexcitation in the pathophysiology of Takotsubo cardiomyopathy. Does cardiac sympathetic function normalize in patients following Takotsubo cardiomyopathy? In this study, heart rate variability was assessed 3 days after the initial event, and surrogates of sympathetic traffic were still different between groups. Serial Holter monitoring could provide insights into whether these patients ever fully revert to normal sympathetic traffic, and the time course of that normalization. It is also not clear if the cardiac sympathetic nerve damage, visualized on ¹²³I-MIBG scan, recovers or not. While left ventricular function usually recovers fairly rapidly, sympathetic damage might still exist. The cardiac wall motion and sympathetic innervation can be discordant, as has been reported in patients with Parkinson Disease¹⁹. This could be assessed with serial cardiac ¹²³I-MIBG scans following recovery of left

ventricular function in patients with Takotsubo cardiomyopathy, a test that may soon be more available for clinical use in the USA based on the ADMIRE-HF study ²⁰. Another question raised by this study is why is there excessive localized sympathetic nerve stimulation? Is it due to a focal seizure ²¹? This hypothesis could be tested using an animal model of Takotsubo cardiomyopathy, perhaps using the rat immobilization model ²². The suggestion that differential activation of the unilateral stellate ganglion may cause Takotsubo cardiomyopathy also suggests that stellate ganglionic stimulation might be a viable method to induce Takotsubo cardiomyopathy in an animal model.

It is not clear at this time how one should convert this advanced understanding of pathophysiology to more effective treatments for Takotsubo cardiomyopathy. One could consider treating these patients with central sympatholytic drugs (like clonidine or alpha-methyldopa) or combined alpha- & beta-blockade. This strategy might make more sense if data emerge about ongoing excessive sympathetic nervous system tone. Otherwise, the treatment would result only when the damage has already been completed.

This report by Bonnemeier et al. ¹¹ has furthered our understanding of the pathophysiology of Takotsubo cardiomyopathy. To paraphrase Socrates, the more I learn, the more I learn how little I know.

Acknowledgments

Funding: Supported in part by NIH grants K23 RR020783, R01 HL102387, P01 HL56693, UL1 RR024975, and the Paden Autonomic Dysfunction Center.

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