JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 8, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.01.026

EDITORIAL COMMENT

Cardiac Sympathetic Disturbance in Takotsubo Cardiomyopathy

Primary Etiology or a Compensatory Response to Heart Failure?*

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The clinical and ventricular wall motion abnormality features of takotsubo cardiomyopathy are well defined. However, the underlying pathophysiology of this disorder is not completely understood. It has been suggested that takotsubo is a clinical syndrome with a multitude of predisposing factors, triggers, and pathogenic mechanisms, whose common final outcome is transient left ventricular systolic dysfunction characterized by "apical ballooning" with relative sparing of the basal segments. The syndrome is often preceded by acute stress (somatic and/or emotional) followed by chest pain, electrocardiographic abnormalities, and elevated cardiac troponin levels in the absence of obstructive coronary artery disease.

Massive catecholamine release and exaggerated sympathetic activation with elevated plasma catecholamines (up to 3-fold higher compared with patients presenting with acute myocardial infarction) are thought to play pivotal roles in the pathophysiology of takotsubo cardiomyopathy (1). Direct catecholamine excess has been shown to cause myocardial stunning and transient contractile dysfunction in both experimental animals and human subjects. The effects of transient contractile dysfunction may be a consequence of myocardial ischemia from epicardial coronary artery or microvascular vasospasm causing preconditioning and ischemic stunning, which confer protection against subsequent episodes of ischemia and preserve energy metabolites by down-regulating contractile function and metabolism. Such elevated catecholamines may originate from circulating systemic sources (bloodstream), from sympathetic nerve terminals, or from local stores within the heart itself and overload adrenergic receptor signaling systems in certain regions of the heart. Discordant ventricular wall response to catecholamines may result from the heterogeneous β_1/β_2-receptor distribution in the left ventricular myocardium, with a postulated base-to-apex β_2-adrenoreceptor gradient that makes the apex more vulnerable to exaggerated catecholamine surges (2). Radiotracers that target cardiac sympathetic activity, such as the norepinephrine analogue, iodine-123-*meta*-iodobenzylguanidine (*m*IBG), may provide insight into the presence and distribution of sympathetic nerve terminals in the left ventricular myocardium in relation to regional wall motion abnormalities in the acute, subacute, and recovery phases of the takotsubo syndrome. The *m*IBG images may be supplemented with myocardial perfusion and metabolic imaging studies to garner information on myocardial ischemia, infarction, and metabolic stunning (3,4).

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In this issue of *iJACC,* Christensen et al. (5) report on a study that prospectively evaluated cardiac sympathetic activity by *m*IBG scan and blood catecholamine levels in 32 patients with takotsubo cardiomyopathy and 20 control subjects in subacute (6 to 10 days after presentation with acute coronary syndrome) and recovery phases (4 months later). The study was designed such that the "disease pattern" of the control group mimicked that of takotsubo cardiomyopathy. Accordingly, Christensen et al. (5) prospectively evaluated cardiac sympathetic activity by *m*IBG scan and blood catecholamine levels in subjects who presented with initial symptoms and signs closely mimicking those of takotsubo cardiomyopathy with suspicion of ST-segment elevation

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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JACC: CARDIOVASCULAR IMAGING, VOL. 9, NO. 8, 2016
AUGUST 2016:991–3

acute coronary syndrome. The control group did not exhibit apical ballooning on the left ventriculogram or transthoracic echocardiography but had elevated levels of both troponin T and creatine kinase MB (nontransmural myocardial infarction or myocarditis). The major findings were that patients with takotsubo cardiomyopathy showed cardiac hypersympathetic activity (decreased heart-to-mediastinal [H/M] ratio and increased washout rate on *m*IBG scan) in the subacute phase, compared with their recovery phase at 4 months. Patients with takotsubo cardiomyopathy also exhibited higher sympathetic activity than control subjects during the subacute phase, but not in the follow-up recovery phase. Plasma epinephrine levels were increased in patients with takotsubo cardiomyopathy in the subacute phase, when compared both with their follow-up recovery phase and with control subjects in the subacute phase. There was no difference in norepinephrine levels.

The findings of this report support the hypothesis that the sympathetic nerve system and/or endogenous catecholamines may play a role in the disease pathogenesis. Although it is unlikely that *m*IBG will have a new clinical indication for assessing patients with takotsubo cardiomyopathy in the acute or subacute setting, this relatively large prospective study from a single center does make an important contribution to the literature.

Although other investigators have applied *m*IBG in smaller numbers of subjects with takotsubo cardiomyopathy, the current study included a cross-sectional comparison control group. Moreover, this large prospective study performed a longitudinal comparison of patients with takotsubo cardiomyopathy in the subacute and recovery phases.

The control subjects consisted of a heterogeneous group of patients with myocarditis or aborted infarction who were not necessarily in heart failure. This was reflected in the significant difference between the mean left ventricular ejection fraction (LVEF) of patients with takotsubo cardiomyopathy (32 ± 2%) compared with the LVEF of subjects in the control group (51 ± 11%). Thus, it is conceivable that the observed differences in the *m*IBG indices (H/M ratio and washout rate) in the subacute phase between the patients with takotsubo cardiomyopathy and the control subjects simply reflected differences in LVEF and heart failure in the 2 groups. However, a longitudinal comparison of the subacute and recovery phases in the patients with takotsubo cardiomyopathy showed improvement in both H/M ratio and washout rate. Importantly, the H/M ratio (2.42 ± 0.45) and washout rate (33 ± 14%) of patients with takotsubo cardiomyopathy in the *recovery phase* were similar to the H/M ratio (2.34 ± 0.6) and washout rate (33 ± 19%) of control subjects in the *subacute phase*. This finding provides credence to the concept that exaggerated sympathetic activation with elevated plasma catecholamines plays a pivotal role in the pathophysiology of takotsubo cardiomyopathy. However, the *m*IBG scan was performed at the subacute phase, not before or at the onset of the disease. Consequently, whether cardiac sympathetic disturbance is the primary cause and trigger of Takotsubo cardiomyopathy or simply a compensatory response to heart failure cannot be differentiated with the current data.

EXPERIMENTAL EVIDENCE FOR CARDIAC SYMPATHETIC DISTURBANCE

During physiological conditions, sympathetic nerves release mainly norepinephrine, which stimulates postsynaptic myocyte β_1-receptors, exerting a positive inotropic effect through G_s-coupling protein. Epinephrine in the myocardial sympathetic clefts is mainly diffused from the coronary circulation, which also binds to β_1-receptors and activates this positive inotropic response. Similarly, myocytes express β_2-receptors, which have 2 binding sites (high and low affinity) for epinephrine. Binding of epinephrine to high-affinity sites stimulates the G_s protein, whereas binding to the low-affinity site triggers the G_i protein. At a high epinephrine level, when the high-affinity sites are fully bound, the low-affinity binding sites become functional (6). The binding of the low affinity sites triggers the switch from G_s to inhibitory G_i coupling and causes a negative inotrope, leading to apical ballooning. After the epinephrine surge is cleared from the circulation and myocardial sympathetic clefts, β_2-G_i coupling either switches back to G_s coupling or is internalized and degraded, thereby enabling myocytes to recover their inotropic function. This finding may explain the reversible wall motion abnormality and recovery of ventricular function in patients with takotsubo cardiomyopathy.

The basis of this hypothesis is an assumption that the density of β_2-receptors is higher in the apical region, as has been demonstrated in a rat model (7). However, it is unclear whether the human heart has a similarly decreased gradient of β_1/β_2-receptor ratio from the basal to the apical area. Increasing reports of an atypical or "inverted Takotsubo" pattern of the disease, involving basal, midventricular, and right ventricular myocardium, challenge the β_1/β_2-receptor gradient hypothesis. Direct measurement of the β_1/β_2-receptor gradient in the human heart is thus essential,

but difficult, because of ethical issues with tissue biopsies from different regions of a healthy heart.

CONCLUSIONS

Takotsubo cardiomyopathy is associated with increased cardiac sympathetic activity, and it is most likely induced by a discordant regional wall motion response to high epinephrine levels secondary to switching from G_s to G_i coupling of β_2-receptors at the middle to apical region. Alternatively, the disease could be caused by a complex interplay among different factors, including cardiac sympathetic innervation, regional receptor distribution, high circulation catecholamine toxicity, and myocardial ischemia. Imaging data, such as: 1) correlation of regional *m*IBG activity on single-photon emission computed tomography and wall motion; and 2) measurement of β_1/β_2 distribution and function in normal heart with positron emission tomography-radiolabeled specific receptor ligands that can provide in vivo dynamic information of β-receptor distribution and function in the heart, may help to elucidate the pathophysiology of takotsubo cardiomyopathy further.

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KEY WORDS heart failure, iodine-123–*meta*-iodobenzylguanidine (*m*IBG), myocardial stunning, radionuclide imaging, sympathetic innervation, takotsubo cardiomyopathy