# Takotsubo syndrome in the absence of an overt stressor: A glimpse into its mechanistic and clinical aspects

To the Editor,

In the clinical setting, takotsubo syndrome (TS) is well known to be associated with adrenergic discharge mostly attributable to various emotional and physical triggers (1, 2). A recently published article by Taghavi et al. (1) has reported an interesting case of TS in the absence of an apparent stressor. This form of TS might be termed as "spontaneous TS" and might potentially mimic other cardiovascular conditions including myocarditis clinically (1). Accordingly, a few comments were made on this interesting case particularly emphasizing on its mechanistic and clinical implications:

First, evolution of "spontaneous TS" might be related to certain mechanical factors regardless of existing stressors particularly in patients with preexisting hypertensive heart disease or hypertrophic cardiomyopathy (HCM) (2, 3). That is, sudden increases in midventricular gradient (MVG) (possibly due to abrupt physiological changes) might elicit myocardial stunning in the left ventricular (LV) apical segments (leading to an apical ballooning pattern) possibly as a consequence of excessive myocardial wall tension in these segments (2). Therefore, the evolution of TS in this case (1) seemed possible to have a potential mechanical basis (2, 3). In this case, right ventricular (RV) dysfunction on initial echocardiogram might have been a secondary pathology (rather than direct TS involvement) associated with substantial LV morphological changes induced by the TS episode. Accordingly, we wonder whether the severity of left ventricular hypertrophy was also assessed along with resting and provoked MVG (if any) values in the patient.

Second, "spontaneous TS," though less likely, might also emerge due to subtle pathologies of the central or peripheral nervous system leading to bouts of adrenergic storm. In particular, involvement of the cardiovascular center in the brain stem (medulla oblongata) might potentially trigger TS episodes in the setting of multiple sclerosis (4), and possibly other central neurological conditions even if they are subclinically presenting with vague or no neurological deficit. Accordingly, we wonder whether any subtle neurological findings on physical examination or on imaging modalities were considered along with potential findings suggestive of an autonomic neuropathy (bouts of hypertension, diaphoresis, etc.) in the patient.

Lastly, "spontaneous TS" might rarely arise as a complication of acute myocarditis (5) that initially goes undetected due to its mild symptomatology. Accordingly, the disease process in this case (1) might have commenced as a mild form of myocarditis (as might be consistent with little or no late gadolinium enhancement on imaging) that ultimately turned into a true TS episode during the later stages.

In conclusion; TS without an overt stressor (spontaneous TS) might be regarded as an interesting, yet; potentially underdiagnosed phenomenon with various mechanistic and clinical implications. However, further implications of this phenomenon still need to be established in clinical practice.

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*DOI:10.14744/AnatolJCardiol.2020.84938*

## Author`s Reply

To the Editor,

We appreciate your interest and your comments in this case report detailing differential diagnosis of takotsubo syndrome (TS) especially in the absence of an obvious major stress (1).

TS is well known as the result of forced release of catecholamines secondary to psychogenic or physical stressors (2).

Based on the International Expert Consensus Document on TS, the stressor is not a requisite for the diagnosis of TS (3). Ac-

tually, absence of stressors has been reported in about one-third of patients with TS (4).

The pathophysiology of TS involves two main factors: first, the cognitive centers of the brain, the HPA (hypothalamic-pituitary-adrenal) axis, and the amount of catecholamines that are released in response to a stress and, second, the response of the cardiovascular and sympathetic nervous systems to this catecholamine surge (5). Based on these facts, the level of each component could be different among individuals leading to a wide variation of manifestations between them. Simply put, the threshold of that stressor could be lower in some patients.

Considering these facts, the term "spontaneous TS" seems inappropriate due to possible undetermined causal agents.

In fact, this patient had a familial quarrel before the presentation that could not be categorized as a major stress, but it might be severe enough for her which induced the takotsubo phenomenon.

This patient had no history of hypertension or evidences of hypertrophic cardiomyopathy, including septal hypertrophy and small left ventricle cavity. Any mid cavity gradient in the left ventricle was not detected during evaluation of the patient by echocardiography or ventriculography.

Any neurologic abnormality or any finding suggestive of autonomic disorder was not observed. However, the absence of these disorders was not observed precisely due to the absence of any neurologic sign that leads to further evaluation.

The last proposed mechanism also seems somewhat unusual due to some reasons: First, absence of robust evidences indicating myocarditis; second, extensive involvement of both ventricles that seems not in favor of mild form of myocarditis; third, complete resolution of cardiovascular magnetic resonance findings and absence of myocarditis evidences including late gadolinium enhancement; and finally, absence of myocarditis is one of the TS diagnostic criteria (6). In fact, if the patient had any evidence of possible myocarditis, the diagnosis of TS might be under debate and questionable. However, this mechanism was not completely ruled out as a triggering factor considering that possible coexistence of these two conditions makes the diagnosis more challenging even more due to different therapeutic and prognostic implications (7).

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