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REPLY

Microcirculatory dysfunction and autonomic disturbance in Takotsubo syndrome

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We thank Drs Khalid and Chhabra for their Correspondence (Takotsubo cardiomyopathy and microcirculatory dysfunction. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2015.88)[1] on our Review (Epidemiology and pathophysiology of Takotsubo syndrome. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2015.39),[2] and their contribution to the field. They and others provide clear evidence that, during the acute phase of Takotsubo syndrome and in some patients at follow-up, abnormalities of coronary flow exist when measured indirectly using noninvasive techniques, and indirectly via the Thrombolysis In Myocardial Infarction (TIMI) frame count.

Three important issues should be considered regarding the mechanism they raise in the context of the findings from their studies of TIMI frame count and also those of other studies of coronary flow reserve (CFR). Firstly, whether the abnormalities of coronary flow were present before the acute episode in susceptible individuals, or are sequelae to the acute catecholaminergic storm, is uncertain. Current evidence from Khalid and colleagues supports only the latter, raising the issue of whether the abnormalities detected are causative, secondary but pathophysiologically relevant modifying phenomena, or associated bystander phenomena. A preclinical study of myocardial perfusion before, during, and immediately after the induction of Takotsubo-like apical abnormalities using myocardial contrast echocardiography did not detect any abnormalities of coronary flow or myocardial ischaemia.[3] Although this study has the limitations of being performed in a rat model and using a pharmacological trigger (isoproterenol) rather than endogenous stress, it supports the conclusion that acute catecholamine-induced apical dysfunction, resembling acute Takotsubo syndrome, can occur in the absence of myocardial ischaemia during the acute phase.

Secondly, why such abnormalities of the microvascular circulation should affect only a particular ventricular region rather than the whole ventricle is uncertain, and Khalid *et al.* suggest that the effect might be restricted to the territory of the left anterior descending coronary artery. However, the accepted definition of Takotsubo syndrome or stress cardiomyopathy is regional wall motion abnormalities in more than one coronary artery territory, thereby requiring the microvascular abnormalities—if causative—to extend beyond a single coronary territory. Given that ~20% of patients do not have the classic apical variant—having instead mid left ventricular or basal variants, both with circumferential (multivessel) distribution of the acute regional wall motion abnormalities—how microvascular dysfunction selectively affects these myocardial regions is uncertain.

Finally, an equally important issue is what the reduced TIMI frame count or CFR measured using other noninvasive imaging methods actually represents as a physiological mechanism. The standard view is that reduced CFR is secondary to 'microvascular dysfunction', but reduced coronary flow in unobstructed coronary arteries might equally reflect abnormalities of myocardial relaxation during diastole, leading to reduced 'suction wave'-driven coronary flow.[4] Szardien *et al.* reported an important histological finding that endomyocardial capillary density is reduced owing to the expansion of the extracellular matrix after the acute episode of Takotsubo syndrome.[5] The investigators reported a decreased vascular bed in the myocardium in patients after Takotsubo syndrome. This structural alteration could also result in the reduced coronary blush disturbance of contrast media represented by TIMI frame count.

We fully agree with Khalid and colleagues that microcirculatory dysfunction might exist in patients during Takotsubo syndrome. However, the question of cause versus consequence, for the reasons discussed above, means that microcirculation abnormalities as the cause of Takotsubo syndrome has not been proven and, in our view, is not a strong candidate for the causative pathophysiology. In our Review, we emphasize that an underlying mechanism exists for the onset of this syndrome, particularly in the brain–heart connection. Excessive hypothalamic–pituitary–adrenal (HPA) gain and epinephrine release are thought to be one of the causes of Takotsubo syndrome. Although evidence indicates that catecholamines usually act as a vasodilatory agent in the coronary vessels, a large amount of catecholamines induces endothelial impairment of these vessels after oxidative stress, which could result in the abnormalities of the microcirculation observed. We thank Khalid and Chhabra for raising this issue, and much remains to be understood about the pathophysiology of Takotsubo syndrome, during both the acute episode and the aftermath.

We also thank Dr Madias for his Correspondence (Autonomic nervous system and a 'vascular phase' in Takotsubo syndrome pathogenesis. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2015.89)[6] on our Review,[2] and his positive comments. We agree that a number of pathophysiological phenomena exist, and that these can occur simultaneously or sequentially in the cardiovascular system in the aftermath of the catecholamine storm. We do not suggest that β2-adrenoceptor stimulus trafficking to $G_{\alpha i}$ is incompatible with toxicity. Instead, excessive activation of the β1-adrenoceptor and β2-adrenoceptor $G_{\alpha s}$ pathways—known to be cardiotoxic—can be dampened by β2-adrenoceptor $G_{\alpha i}$, which limits but does not completely prevent the toxicity, resulting in a rise in cardiac troponin levels in the majority of patients. However, the recovery of macroscopic myocardial function in survivors would suggest that permanent injury or toxicity is limited, although growing evidence supports longer-term abnormalities of myocardial metabolism and function at follow-up.

We agree that whether both the abnormalities of 'microvascular function' and the 'coronary vasospasm' reported are causative, epiphenomena, or perhaps modifiers is currently uncertain. Vasospasm, which can also be considered a superimposed ischaemic insult, might occur in some patients and, therefore, we decided to include it in our multifactorial pathophysiological model (see discussion of microvascular dysfunction above).

We agree with Madias that an autonomic disturbance, or storm, might be the initiating trigger in many patients. This mechanism is compatible with the catecholamine hypothesis, because the sources of the high catecholamine surge are the sympathetic nerves and the adrenal gland—both of which are effector arms of the sympathetic branch of the autonomic nervous system. With the rare exception of phaeochromocytoma, emotional or physical stresses would activate the sympathetic storm observed via the HPA axis leading to the surge in circulating catecholamines, in addition to local release from the cardiac sympathetic nerve endings.

Madias raises the intriguing question of whether abnormalities of the autonomic nervous system, such as diabetic neuropathy, could be protective. We agree that any alteration of the autonomic nervous resulting in reduced sympathetic tone or gain of the HPA axis in response to stress could be considered potentially protective. However, we would urge caution, because in many reported examples of patients with Takotsubo syndrome the trigger was an acute neurological illness known to involve autonomic dysfunction, such as acute Guillain–Barré syndrome or acute systemic lupus erythematosus crisis, in which autonomic dysfunction leads to turbulence and excessive sympathetic tone or gain. Deshmukh and colleagues have reported the largest cohort of patients with Takotsubo syndrome from the US Nationwide Inpatient Sample.[7] Despite the limitations of their retrospective approach, they provide the largest epidemiological cohort. In their initial report from 2012, a subtly reduced incidence of diabetes mellitus in patients with Takotsubo syndrome is suggested.[7] However, this trend is in comparison to all hospitalized patients in the control group, and diabetes is clearly a driver of many acute medical and surgical emergencies necessitating hospitalization. Therefore, these data do not support the conclusion that diabetes is protective, but we understand the logic underpinning the proposed hypothesis, and more studies and research are clearly required to investigate whether blunted autonomic responses are protective against the development of Takotsubo syndrome in the context of stressful triggers.

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Competing interests
The authors declare no competing interests.

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