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Is High-Dose Catecholamine Administration in Small Animals an Appropriate Model for Takotsubo Syndrome?

To the Editor:

The recent review article by Wright and colleagues¹ of the takotsubo syndrome (TTS) provides an opportunity to discuss a complex and persistently perplexing clinical entity. It is laudable that these investigators are working to devise an experimental animal model of TTS that could explain the mechanism and clinical manifestations of this mysterious disease.

The project appears to be based on the assumption that TTS is a “normal” pathophysiological response to certain noxious pharmacologic agents and that this response is experimentally reproducible in any animal. We would argue that this has not yet been proven, for 2 main reasons.

1. The authors’ model of TTS (and similar experimental models^{1–4}) do not share certain essential aspects of clinical human TTS.

(a) Whereas there are multiple predisposing and/or precipitating factors in human TTS, a single, essential common initiating factor has never been substantiated, including high catecholamine levels. Although the catecholamine “surge” is frequently claimed to be fundamentally important, no clinical guideline has ever required clinicians to measure catecholamine levels routinely, nor are they empirically reported in most published clinical studies. Furthermore, no large-scale study has ever correlated the development of TTS with catecholamine blood levels in non-TTS patients who present with any critical clinical conditions (and, presumably, high catecholamine levels). Catecholamines could be a factor, but they are not the only one at play in TTS.

(b) The reproducibility of TTS has never been tested in patients who receive drug regimens presumed to precipitate TTS, such as dobutamine testing, therapeutic administration of other catecholamine vasopressors, and chemotherapy. If an animal model of TTS caused by catecholamines is to be considered valid, one should be able to demonstrate the typical disappearance of the same response inducibility after its first occurrence. The catecholamine theory as currently stated suffers from a fundamental contradiction: It assumes that catecholamine overloading results in a TTS-like response, but it does not explain why TTS does not recur in patients whose stress or catecholamine levels usually remain high or increase after the initial presentation.

(c) Severe hypertension is very rarely reported in patients during the initial phase of TTS. This is surprising, because pheochromocytoma and subdural hematoma (which are typically accompanied by hypertension and occasionally by genuine forms of TTS, on phenotypic grounds) have been excluded from inclusion in the definition of TTS. The incidence of TTS is reported to be only approximately 5% in clinical pheochromocytoma patients.⁵

(d) The mortality associated with experimental TTS induced with high-dose catecholamine administration in small animals

(rats and mice) has been in the range of 15–40%.^{1–3} This is not comparable to the mortality rate in human patients with TTS (1–3%). This difference suggests that the doses used experimentally are in the toxic range.

(e) Experimental models may have some echocardiographic and/or electrocardiographic resemblance to TTS, but it is difficult to assess those features (apical ballooning) in a small animal heart, beating at more than 300 beats/min (see Figure 1¹).

2. The review article¹ concludes that clinical TTS must be a product of catecholamine overload, but TTS more closely resembles “stunned myocardium” (severe, localized reversible dysfunction). The authors quickly dismiss coronary spasm, the usual explanation for stunning, as an explanation for TTS; however, there is recent human evidence (although only from pilot studies) to suggest that endothelial dysfunction with coronary spasm may indeed play an essential, causal role in TTS. Recent studies even show the experimental reproduction of TTS in recovering patients, as assessed by acetylcholine (ACh) testing of endothelial function.^{6,7} Systematic use of ACh testing in the recovery phase of TTS has shown repeatedly that ACh induces intense spasm of the related territories, accompanied by reproduction of TTS in the myocardial segments originally affected.⁶ This spasm (and left ventricular dysfunction) is promptly and consistently eliminated by intracoronary administration of nitroglycerine.

An appropriate experimental animal model of TTS must address these important features of TTS. Toxic doses of catecholamines are not likely to be helpful in creating such a model, as they seem to cause more sustained and profound myocardial changes than those associated with TTS.

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