



## Editorial

## What can we learn from animal models of Takotsubo syndrome?

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The current Journal issue includes an extensive report by Ali et al. [1] on a rat model of Transient Takotsubo Syndrome (TTS) that illustrates the complexity of attempting to simulate human pathology in animal “equivalents”. Clearly, the medical community continues to be frustrated by our persistent ignorance on TTS etiopathogenesis and should continue to strive to clarify a disappointingly inadequate “explanation” of this unique rare pathology. The present editorial attempts to summarize current thoughts on the subject matter.

- Any animal experimentation should attempt to clarify one or more specific and clear questions, that can potentially be explored by such model.
- Experimental models of TTS, for complex and confusing that it continues to appear, must be characterized by consistent features, that we can consider “common” denominator to most forms of the clinical entity being investigated. We suggest:
  - a) TTS involves sudden onset of transient symmetrical left ventricular (LV) dysfunctional area [2] (involving about 35% of LV) [3], and gradual, spontaneous resolution “ad integrum”, in a few-days span. Evolving ST-T changes is frequently present [2,3].
  - b) Some variable predisposing or precipitating factors are potentially accompanying TTS onset. Generally, no consistent and recognized, treatable causative factors can be currently recognized.
  - c) Rarely, TTS recurs: evidence of a frequent “self-vaccination” effect of one episode [S1].
  - d) The most frequent and characteristic form of TTS features apical ballooning dyskinesia (80–90% of cases).
  - e) A catecholamine surge (as evidenced by “high” serum levels of endogenous or therapeutic catecholamines, but rarely by tachycardia and hypertension) may or may not be involved in triggering

an episode of TTS [4]. Pain, suffering, emotional stress may be present (50–70% of cases) [3,S-1].

- f) Sometimes, an acetylcholine (Ach) test of endothelial dysfunction (leading to diffuse and severe spasm) performed close after an event of TTS can lead to reproduction of both chest pain, ST changes, coronary spasm of many branches and left ventricular functional changes reproducing the presenting form [2,S-2]. Such events can be quickly resolved by intra-coronary nitroglycerine infusion. Only a few recovering TTS patients will have a positive Ach test followed by a high probability of TTS recurrence. Nitroglycerine administration quickly leads to aborted presentations (no residual LV dysfunction). Ach test is the only known method to reproduce relapses of TTS on clinical grounds.
- g) Mortality is rare after hospital admission, but some TTS patients have sudden cardiac death during the first hour since presentation in extra-hospital environment [5]. No specific autopsy findings have been reported to establish the diagnosis of TTS [S-3].

Ali et al. [1] have tried to test the possibility to reproduce TTS (reproduction of the abovementioned features) under the effects of high doses of catecholamines in rats models. Such approach is similar to the study of patients submitted to therapeutic administration of catecholamines or clinical cases of pheochromocytoma [6,7], which should: 1. Use of dobutamine in stress testing or vasopressors in hypotensive/shock syndromes quite rarely induce TTS. 2. Pheochromocytoma patients are frequently observed during many years, while suffering recurrent spells of catecholamine crises quite rarely they become victims of TTS, but some will develop diffuse, partially-irreversible chronic cardiomyopathy [6,7]. At this regard, especially relevant is the recent, accurate metanalytic review of the catecholamines in TTS by Y-Hassan et al. [8]: definitively, the original report by Wittstein et al. [4] (suggesting a generalized presence of “massive” catecholamines surge in patients with TTS) was incorrect. In this author's conclusion, catecholamines could be “triggering” more than “causing” TTS. Additionally, prior general-population studies of serum catecholamines in stressful conditions showed only mild variations, or 2–3 times the baseline levels [S-4], even though we must recognize that nerve ending release may not be accounted for by serum levels [9].

### 1. The Ali et al. studies [1, S-5]

The present article focused on the effects of large doses of isoprenaline (50 mg/kg) [1] in 295 rats (essentially, intraperitoneal isoprenaline

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whose LD50 is 128 mg/kg) [S-6]. The experiments were reported as characterized by the following results:

- a.) High-dose catecholamines, but also inotropes (like milrinone) can cause similar pattern of transient myocardial apical dysfunction similar to what TTS causes in human. Mean area of akinesia is 10–20% of total LV (at heart rate of 600/min).
- b.) Preliminary administration of high-dose Beta-receptor antagonists (metoprolol and propranolol) prior to isoprenaline decreases the catecholamine effect.

Our persistent question [S-7] is if this and similar rat models [10] really duplicate the human TTS entity or only the toxic effects of catecholamines, used at very high dosages. We do not recognize in such model most of the TTS features (above-mentioned 7 characteristic). The experiments seem to cause isoprenaline toxicity, more similar to the pathology seen in pheochromocytoma chronic cardiomyopathy [6,7], than in TTS. Such difference is quite important in evaluating the clinical meaning of similar investigations. We realize that the authors claim that their prior studies [S-5] suggested similarity to clinical TTS by histological documentation (and some reversibility), but we are not totally convinced of such conclusion since the studies' documentation is so limited. Especially, the 33–42% mortality rate of these experiments is quite suggestive that the LV dysfunction is likely due to severe acute drug toxicity, more than TTS-like pathology (which features more extensive and essentially reversible akinesia) [1,10].

Clinical investigations of catecholamines in human TTS should probably consider to introduce a new protocol, including: in patients recovering from TTS presentation, under an investigational protocol, a challenge test based on intravenous administration of epinephrine (or metanephrine, half-life of 1–2 min) at therapeutic doses could be done, accompanied by comprehensive monitoring (symptoms, electrocardiogram, echocardiogram). Ideally, coronary angiography during reproduction of the TTS presentation should be also done, implying the opportunity to administer intracoronary nitroglycerine, in case of a positive test for coronary spasm. Such test would be quite relevant for clinical aims (explanation of the mechanism of TTS, prevention of recurrence). In conclusion, we can recall here the fundamental "Koch's postulates" to establish a cause/effect of a given factor in clinical disease, namely: 1) if a potential causative entity (like a pathologic bacterium or catecholamines) is present in a clinical

entity; 2) if it can be applied to a patient being studied; 3) and if applying the potentially causative factor reproduces the clinical entity; 4) then, the potential causative factor can be named the cause of the disease entity.

#### Declaration of conflicts of interest

None.

#### Appendix A. Supplementary data and References

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2019.01.064>.

#### References

- [1] Ali A., Redfors B., Lundgren J., Alkhoury J., Oras J., Gan L.M., Omerovic E. Effects of pretreatment with cardiostimulants and beta-blockers on isoprenaline-induced takotsubo-like cardiac dysfunction in rats. *Int. J. Cardiol.*, <https://doi.org/10.1016/j.ijcard.2018.12.045>.
- [2] P. Angelini, Transient left ventricular apical ballooning: a unifying pathophysiological theory at the edge of Prinzmetal angina. *Catheter. Cardiovasc. Interv.* 71 (2008) 342–352.
- [3] C. Templin, J.R. Ghadri, J. Diekmann, et al., Clinical features and outcomes of takotsubo (stress) cardiomyopathy, *N. Engl. J. Med.* 373 (2015) 929–938.
- [4] I.S. Wittstein, D.R. Thiemann, J.A. Lima, et al., Neurohumoral features of myocardial stunning due to sudden emotional stress, *N. Engl. J. Med.* 352 (2005) 539–548.
- [5] P. Angelini, C. Uribe, Cardiac arrest in takotsubo cardiomyopathy, *Am. J. Cardiol.* 116 (2015) 489–490.
- [6] N. Gagnon, S. Mansour, Y. Bitton, I. Bourdeau, Takotsubo-like cardiomyopathy in a large cohort of patients with pheochromocytoma and paraganglioma, *Endocr. Pract.* 23 (2017) 1178–1192.
- [7] M. Batisse-Lignier, B. Pereira, P. Motreff, R. Pierrard, C. Burnot, C. Vorilhon, et al., Acute and chronic pheochromocytoma-induced cardiomyopathies: different prognoses?: A systematic analytical review, *Medicine (Baltimore)* 94 (2015) e2198, <https://doi.org/10.1097/MD.0000000000002198>.
- [8] S. Y-Hassan, Plasma epinephrine levels and its causal link to takotsubo syndrome revisited: critical review with a diverse conclusion, *Cardiovasc. Revasc. Med.* (2018) <https://doi.org/10.1016/j.carrev.2018.10.026>.
- [9] A.R. Lyon, P.S. Rees, S. Prasad, P.A. Poole-Wilson, S.E. Harding, Stress (takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning, *Nat. Clin. Pract. Cardiovasc. Med.* 5 (2008) 22–29.
- [10] J. Sachdeva, W. Dai, R.A. Kloner, Functional and histological assessment of an experimental model of takotsubo's cardiomyopathy, *J. Am. Heart Assoc.* 3 (2014), e000921. <https://doi.org/10.1161/JAHA.114.000921>.