LETTER TO THE EDITOR

Estrogens for protection from an index and recurrent episodes of takotsubo syndrome?

John E Madias^{1,2}¹Icahn School of Medicine at Mount Sinai, New York, USA²Division of Cardiology, Elmhurst Hospital Center, Elmhurst, New York, USACorrespondence should be addressed to J E Madias: madiasj@nychhc.org*Journal of Endocrinology*
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To the Editor

The fascinating article of [Fu *et al.* \(2021\)](#), published in the June 2021 issue of *Journal of Endocrinology* pages 209–222, brings up again the vexing problems of prevention and therapy of takotsubo syndrome (TTS) ([Madias 2019, 2021](#)). As the authors state there are no 'conventional' such therapies, and what are available 'are not effective' (1); if one considers TTS as a malady associated with a transiently 'stunned' myocardium, some other therapies designed for ischemic coronary syndromes, including acute myocardial infarction have been recently proposed, and may need to be evaluated and tried in patients with TTS ([Madias 2021](#)). The authors ([Fu *et al.* 2021](#)) report on the protective mechanism of the G protein-coupled estrogen receptor (GPER) activation on the epinephrine (Epi)-induced TTS, employing their adult rat model and a human-induced pluripotent stem cells-derived cardiomyocytes (hiPSC-CM) preparation; their work echoes some of the findings of [Ueyama *et al.* \(2003\)](#), [Ueyama \(2007\)](#), dated almost 20 years ago. Such investigations only explain why TTS emerges mainly in women and particularly of the postmenopausal age, and reveals that estrogens exert a cardioprotective effect, preventing the emergence of TTS ([Ueyama *et al.* 2003](#), [Ueyama 2007](#), [Fu *et al.* 2021](#)), which is very important from the pathogenesis point of view. Although estrogen therapy is not currently recommended, particularly for women in their 60s and 70s, the time period during which postmenopausal women are at high risk to develop TTS, one wonders whether low-dose or transdermal estrogens ([Pinkerton 2020](#)) may have a protective effect on the occurrence of TTS, or after an index episode of TTS, prevention of its recurrence(s). The authors showed that the GPER activation with agonist G1/E2 prevented the increase in the end-systolic left ventricular internal diameter and the decrement of the left ventricular

ejection fraction in their rat model, and the shortening of the hiPSC-CM amplitude, among a large host of other supportive findings of G1/E2-induced cardioprotection in Epi-elicited TTS (1). Relevant to the above therapy proposition of low-dose estrogens for the prevention of TTS in women is whether, experiments employing the author's rat model, a dose of 12 µg/100 g or 24 µg/100 g, instead of the used 48 µg/100 g G1 ([Fu *et al.* 2021](#)), exerts a significant cardioprotective effect if administered 10 min prior to the Epi-elicited TTS. Even more relevant to the human TTS may be an implementation of the authors' model of adult rats ([Fu *et al.* 2021](#)), but after the rats are ovariectomized, and while they are receiving chronic estrogen supplementation ([Ueyama *et al.* 2007](#)), in low-doses, prior to Epi-elicitation of TTS. I will greatly appreciate the response of the authors on the above.

Declaration of interest

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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