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NEW RESEARCH PAPER

# Nitrosative Stress as a Modulator of Inflammatory Change in a Model of Takotsubo Syndrome

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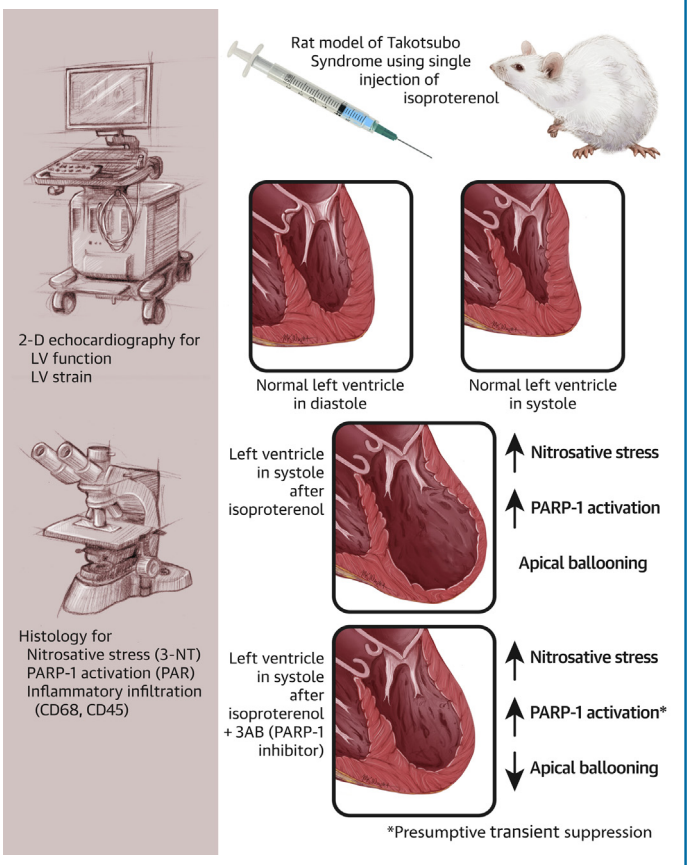
## VISUAL ABSTRACT

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## HIGHLIGHTS

- **Treatment of female rats with a single dose of isoproterenol results in apical hypokinesis mimicking Takotsubo syndrome**
- **Myocardial inflammation includes increased content of 3-nitrotyrosine and poly(ADP-ribose), indicating nitrosative stress and poly(ADP-ribose) polymerase-1 (PARP-1) activation, respectively**
- **Pretreatment with 3-aminobenzamide (a PARP-1 inhibitor) attenuates negative inotropic changes**
- **We conclude that the peroxynitrite/PARP-1 cascade contributed to negative inotropy in this model of Takotsubo syndrome, consistent with the limited data available in patients**

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**ABBREVIATIONS AND ACRONYMS**

**3AB** = 3-aminobenzamide

**3-NT** = 3-nitrotyrosine

**ANOVA** = analysis of variance

**ISO** = isoproterenol

**LV** = left ventricular

**NFκB** = nuclear factor kappa B

**NO** = nitric oxide

**NOS** = nitric oxide synthase

**$O_2^-$** = superoxide

**$ONOO^-$** = peroxynitrite

**PAR** = poly(ADP-ribose)

**PARP-1** = poly(ADP-ribose) polymerase-1

**TS** = Takotsubo syndrome

**TXNIP** = thioredoxin-interacting protein

**SUMMARY**

Previous studies have shown that patients with Takotsubo syndrome (TS) have supranormal nitric oxide signaling, and post-mortem studies of TS heart samples revealed nitrosative stress. Therefore, we first showed in a female rat model that isoproterenol induces TS-like echocardiographic changes, evidence of nitrosative stress, and consequent activation of the energy-depleting enzyme poly(ADP-ribose) polymerase-1. We subsequently showed that pre-treatment with an inhibitor of poly(ADP-ribose) polymerase-1 ameliorated contractile abnormalities. These findings thus add to previous reports of aberrant β-adrenoceptor signaling (coupled with nitric oxide synthase activation) to elucidate mechanisms of impaired cardiac function in TS and point to potential methods of treatment. (J Am Coll Cardiol Basic Trans Science 2018;■:■–■)


Takotsubo syndrome (TS) reflects catecholamine-induced global myocardial inflammation, which predominantly affects the left ventricular (LV) apex. Since its initial description by Japanese investigators (1), the phenomenon of TS has aroused considerable interest among clinicians, as its differentiation from acute myocardial infarction represents a diagnostic challenge (2,3). Even more intriguing is the epidemiology of TS, with its predominant occurrence in aging women, episodes being precipitated both by acute emotional or physical stressors and the presence of neuropsychiatric disorders (4,5). Furthermore, it was originally considered that TS might be a relatively rare disorder, which is not the case: approximately 10% of suspected ST-segment elevation myocardial infarction cases in women aged >50 years are actually TS (6). Finally, TS induces prolonged myocardial inflammation (7), including patchy inflammatory infiltrate on myocardial biopsy samples (8), with persistent LV dysfunction (9), disordered cardiac energetics (10), and associated impairment of quality of life for ≥3 months, with a propensity toward recurrence (11).

To date, the only definitive progress that has been made regarding the pathogenesis of TS is related to the pivotal role of catecholamine release and its interactions with the myocardium: there is extensive evidence that TS can be induced by both endogenous and exogenous catecholamines (12). Furthermore, considerable evidence exists that the effects of this catecholamine "surge" on the myocardium include an initial phase of regional depression of myocardial contractility (with minimal myocardial necrosis) followed by a prolonged phase of slowly resolving intense and essentially global myocardial inflammation and associated edema. Among systemic markers of myocardial inflammatory activation, substantial release of B-type natriuretic peptide/N-terminal pro-B-type natriuretic peptide in the absence of pulmonary edema serves best to delineate the progress of attacks (13). However, the precise cause of this inflammatory activation remains uncertain.

Studies in rodent models of TS have added substantially to the understanding of the impairment of myocardial contractility and associated propensity toward shock in the acute phases of the disorder. Notably, 2 studies have suggested a pivotal role for stimulation of $\beta_2$-adrenoceptors, with an associated shift from Gs- to Gi-based signal transduction, mediating cardiodepressant (but also cardioprotective) effects (14,15). However, the findings of these investigations do not address the issue of the pathogenesis of the myocardial inflammation that follows the initial catecholamine exposure, nor has any mechanism for inflammatory activation in TS been suggested by other previous experiments.

We made a series of observations which suggest that nitrosative stress may be critical to both inflammation and energetic impairment in TS. We showed that patients with TS differ from age-matched female

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