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Letters

TO THE EDITOR

There Should Not Be Much Doubt That Neurogenic Stress Cardiomyopathy in Cardiac Donors Is a Phenotype of Takotsubo Syndrome

I read with great interest the paper by Tavazzi et al. (1) about the staggering similarities between neurogenic stress cardiomyopathy in cardiac donors (NSCCDs) and Takotsubo syndrome (TTS); indeed scrutinizing Table 1 of their paper and reflecting on the arguments the authors present should not leave much doubt that NSCCD is a phenotype of TTS (2,3). A large number of studies, both experimental and clinical, starting at the dawn of the previous century and comprehensively reviewed previously (4), reveal that traumatic, chemical, ischemic, hemorrhagic, tumor-related, seizure-induced injury, or irritation of various brain loci lead to cardiac injury, with all the clinical particulars encountered in TTS. The publications referred to and others that have followed that describe transient left ventricular systolic dysfunction (LVSD) in the setting of brain pathology have done so before 1990, when TTS was formally described and the term TTS was coined (3). Also, many articles among the 3,598 articles accessed in PubMed via the MeSH term "takotsubo" as of December 3, 2017, describe cases of patients who experienced TTS in association with brain pathology from a variety of etiologies. Although the pathophysiological mechanism of TTS is still elusive, the injurious impact of the brain on the cardiomyocytes is probably exerted by an autonomic sympathetic nervous system surge and mediated via norepinephrine secretion, rather than by a direct cardiac effect of blood-borne catecholamines (4).

In our efforts to salvage as many of these precious donor hearts manifesting transient LVSD, but eventually suitable for transplantation, and thus desperately needed by our patients with end-stage heart failure, we should act in the context of a working hypothesis that NSCCD and TTS represent identical pathologies. Accordingly, in evaluating possible cardiac donors, we should heed the authors' recommendations to avoid inotropes and vasopressors, optimize preload, use vasopressin if needed, perhaps consider use of T3 hormone, define and implement optimal hemodynamic treatment, avoid dobutamine stress echocardiography, systematize frequent echocardiography monitoring, consider coronary angiography, and carefully screen for pre-existing heart diseases.

It is conceivable that an ongoing autonomic sympathetic storm continues to exert an inexorable deleterious effect on the donor hearts after LVSD has been detected with the initial echocardiogram; thus, monitoring sympathetic activity with frequent testing of blood catecholamines and using available noninvasive technology of the routine electrocardiography limb and chest electrode hook-up (5) may be of value. Indeed, gauging the degree of cardiac sympathetic overdrive may be useful in the use of β-blockers, both cardioselective and non-cardioselective, or of short-acting variety (e.g., esmolol), in case such drugs, previously advocated, need to be discontinued. Also, one wonders what the effect of extracorporeal membrane oxygenation or intra-aortic balloon counterpulsation would be in "nursing" the donor hearts and quickening the reversion of LVSD. These issues indicate that organ-sharing networks need to work toward a systemized management of heart donors, perhaps in suitable critical care units and optimally geographically distributed, where such patients could be transferred, and all of these suggestions tried, researched, evaluated, and decided upon.

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Please note: Dr. Madias has reported that he has no relationships relevant to the contents of this paper to disclose.

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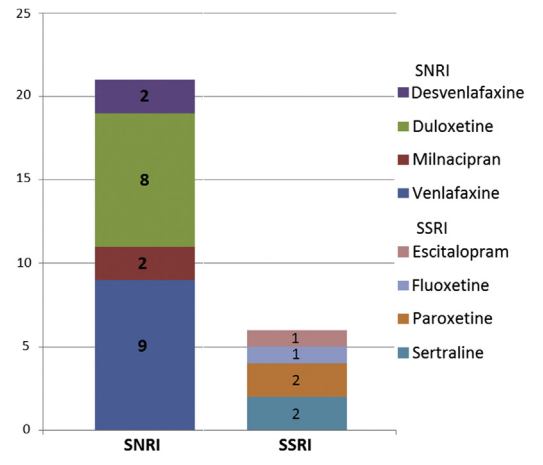
Takotsubo Common Pathways and SNRI Medications

We read with great interest the perspectives of Tavazzi et al. (1) regarding Takotsubo syndrome (TTS), neurogenic stress cardiomyopathy, and the prevailing hypothesis of common catecholamine-mediated pathways. The Division of Pharmacovigilance at the U.S Food and Drug Administration reviewed postmarketing cases of TTS among patients treated with serotonin norepinephrine reuptake inhibitors (SNRIs) compared with selective serotonin reuptake inhibitors (SSRIs) as another possible trigger associated with catecholamine storm and subsequent TTS. We searched the Food and Drug Administration Adverse Event Reporting System database and Medline for all cases of TTS-related adverse events reported with SNRIs or SSRIs submitted through April 11, 2016, meeting Mayo Clinic TTS criteria (2). We identified 21 cases with SNRIs and 6 with SSRIs reporting TTS adverse events (**Figure 1**). TTS developed within the first week of drug initiation or dose escalation in 8 SNRI cases and 1 SSRI case. Case narratives provided information to rule out acute emotional or physical triggers in 10 SNRI cases. Nine SNRI cases reported catecholamine levels, all of which were elevated. None of the SSRI cases reported catecholamine levels. Fourteen SNRI cases developed TTS on doses matching or exceeding the maximum recommended dose, whereas SSRI cases were only reported at doses below the maximum recommended dose. Despite identifying 3.5 times as many SNRI TTS cases relative to SSRI TTS cases, SSRI use has exceeded SNRI use by 4-fold in the National Health and Nutrition Examination Survey database (3). Nonetheless, Food and Drug Administration Adverse Event Reporting System data are subject to under reporting, and total population at risk may be difficult to assess. Confounding by indication remains a concern regarding antidepressants and TTS. Three of our SNRI cases stated only nonpsychiatric reasons for use (fibromyalgia, diabetic neuropathy, urinary incontinence). Additionally, short time to onset, relative absence of emotional or physical triggering events, dose-response relationships, number of cases identified relative to patterns of drug use, and SNRI catecholamine-related mechanism of action are supportive of SNRI-associated TTS, as contrasted with our SSRI cases. The SNRI findings are consistent with the catecholamine storm common pathway noted by Tavazzi et al. (1) SNRI-associated TTS may be a rare event. However, given the seriousness of TTS, practitioners should be aware of the possible association of SNRIs and TTS. SNRI product labels were recently updated to include TTS in adverse reactions (see Section 6.2, Post-Marketing Experience) (4).

FIGURE 1 Food and Drug Administration Adverse Event Reporting System and Medline SNRI and SSRI Cases Associated With Takotsubo Syndrome Adverse Events Through April 11, 2016



There were no citalopram, fluvoxamine, or levomilnacipran cases meeting case series criteria. SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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