cardiomyopathy (TTC), using iodine-123-labeled metaiodobenzylguanidine (^{123}I-MIBG) myocardial scintigraphy and measurements of plasma catecholamines to assess adrenergic activity (1). More in detail, these authors showed in subacute follow-up that TTC was associated with a decreased late heart-to-mediastinum ratio (H/Mlate) and increased washout rate (1). The study concluded that adrenergic hyperactivity has a possible role in TTC (1). The adrenergic hyperactivity plays a central role in TTC (2–5). In fact, in a recent study, Marfella et al. (2) reported the elevation of plasma catecholamines (2- to 3-fold times the normal values for epinephrine and <2-fold for norepinephrine), strengthening the hypothesis that TTC patients may be under a "stress condition" as a triggering mechanism of a more complex cardiomyopathy as TTC. In that study, and as supported by Christensen et al. (1), TTC may be triggered by an altered and not balanced sympathetic tone (2). This may be reflected by augmented catecholamine levels and also assessed by ^{123}I-MIBG in a subacute phase of the disease (1). In Marfella's study catecholamine levels was 758 to 1,240 pg/ml, and this value may be variable under different TTC conditions (2). In fact, the authors have described extremely high plasma catecholamine levels and their metabolite elevations (from the index admission day to days 7 to 9), whereas other patients have shown either normal or slight elevation of plasma or urine catecholamines (3,4). It is our opinion that the hyperactivity of sympathetic tone may be a relevant trigger in TTC (2–5) but that TTC may be due to a complex adrenergic tone and adrenergic receptor altered balance (3–5). This investigated aspect looks to be not less relevant than an isolated adrenergic hyperactivity (1–3). It is our opinion that an altered substrate (adrenergic tone, adrenergic transcriptional receptorial, and molecular pathway alterations) localized to specific left ventricle wall portions (as apex) may condition this clinical condition (2–5). Moreover the catecholamine elevation amount (2 to 3 times or more) represents a trigger mechanism, performing its pathological effect through an altered adrenergic receptorial transcription pathways (2,3) and, in particular, ventricle wall segments (2–5). Therefore, these abnormalities may condition the TTC only for a few myocardial wall areas, such as the apex, leading to an apical ballooning (2–5). This remains the crucial discussion point. At the moment, we cannot replace the receptors involved in altered adrenergic signaling in TTC, but we may try to ameliorate sympathetic tone dysfunction by using antioxidative treatments (2). In further studies conducted in TTC animal models, we could study the adrenergic receptorial transcription processes during hyperadrenergic stimulation. Our opinion, in clinical, and instrumental confirmed TTC cases, remains to find the better treatment trying to restore the autonomic system unbalance in these patients (2). The future hope may be to replace the altered adrenergic receptors pathways and to control the adrenergic tone hyperactivity.

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THE AUTHORS REPLY:

We greatly appreciate the feedback from Dr. Sardu and colleagues on our work (1). As mentioned in the letter, adrenergic hyperactivity is assumed to be the underlying cause of Takotsubo cardiomyopathy, and a possible mechanism has been suggested by Lyon et al. (2). Catecholamines may modulate cardiac function indirectly through the coronary vessels (3,4) or through a direct effect on the myocytes (5). Many different mechanisms may thus contribute to the clinical syndrome of acute catecholamine toxicity. The treatment of Takotsubo cardiomyopathy is still purely supportive, but a causal treatment may be accessible in the future.

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Catecholamine Levels and Cardiac Sympathetic Hyperactivation-Disruption in Takotsubo Syndrome

I read with great interest the work by Christensen et al. (1) and the editorial comment on that study by Chen et al. (2), recently published in *iJACC*. The investigators examined 32 patients with Takotsubo syndrome (TS) and 20 control subjects at the subacute phase and at follow-up examinations, using echocardiography, 123-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy and, plasma catecholamine measurements. Three points deserve discussion in this well-performed study. First, ^{123}I-MIBG scintigraphy has shown uptake defects and high washout rates during the subacute phase in TS patients. This finding is further support to the accumulated evidence for the hypothesis that the local cardiac sympathetic hyperactivation-disruption and norepinephrine seethe and spillover plays a key role in the pathogenesis of TS (3). It is not clear from the study whether the ^{123}I-MIBG scintigraphic defects were restricted to the left ventricular wall motion abnormality regions and whether they were completely normalized during follow-up time. The principle findings of ^{123}I-MIBG scintigraphy in TS in other studies are decreased regional uptake of ^{123}I-MIBG in the hypokinetic/akinetic left ventricular segments and increased washout rate of ^{123}I-MIBG.

Second, plasma catecholamine levels were examined in the study during the subacute phase and at follow-up at 105 days. The authors concluded that one of the most important finding in the study, in addition to the evidence of "myocardial sympathetic hyperactivity," is the increased plasma epinephrine in the subacute phase of the disease and even during follow-up. From the information in the manuscript, one may conclude that plasma epinephrine was normal in control subjects during follow-up ($\log_2$ epinephrine: 4.56 pg/ml; and epinephrine: 24 pg/ml). In such a case and according to the values available in Table 2 (1), there is only mild elevation in plasma $\log_2$ epinephrine during the subacute phase (1.1-fold compared to control patients in the subacute phase and 1.3-fold compared to the control group at follow-up). Such mild elevation of plasma epinephrine may be attributed to marked elevation of plasma epinephrine in only few patients that may result in mild elevation in the whole group. In one study (4), plasma epinephrine was normal in 24 of 27 patients (89%) with TS; moderately elevated (3.8-fold the upper normal limit [UNL]) in 2 patients (7.4%); and markedly elevated (8.9-fold the UNL) in only 1 patient (3.7%). This author would be grateful if the following question were answered by the investigators: what were the normal reference values of plasma epinephrine and norepinephrine in the study? How many patients with TS had normal or nearly normal plasma epinephrine levels? What was the degree of epinephrine and norepinephrine elevations (mild, moderate, or severe)? Are the degrees of plasma catecholamine elevations in the study comparable to the striking elevations reported in the study by Wittstein et al. (see ref. 29 in Christensen et al. [1])?

Third, Chen et al. (2), in a reply letter, raised one important question seen in the title of the comment, which is whether the cardiac sympathetic disturbance in TS is a primary cause or a compensatory response to heart failure. In patients with chronic heart failure, there is extensive evidence for cardiac sympathetic hyperactivity, initially as a compensatory mechanism but with time continuing to cardiac sympathetic