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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

disruption with deleterious consequences (5). In addition to the ^{123}I-MIBG scintigraphic findings in TS, there is extensive evidence, discussed elsewhere (3), supporting the hypothesis of the presence of a causal link between local cardiac sympathetic hyperactivation-disruption (triggered by emotional or physical stress factors) and TS (3). The local cardiac sympathetic hyperactivation-disruption that occurs in patients with chronic heart failure, regardless of the underlying cause, may also be a form of TS occurring in repetitive attacks or in chronic form triggered by heart failure or its severe symptoms. Cardiac sympathetic hyperactivation-disruption is most probably the primary cause of TS (3), and chronic TS with acute exacerbation may be the main cause of acute deterioration of heart failure in patients with chronic heart failure (5).

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THE AUTHORS REPLY:

The authors greatly appreciate the feedback from Dr. Y-Hassan. In the presented study (1), planar iodine-123-labled MIBG (^{123}I-MIBG) was used to assess late heart-to-mediastinum ratio and ^{123}I-MIBG washout ratio. Because single-photon emission computed tomography imaging was not applied, spatial resolution was not sufficient to assess regional cardiac ^{123}I-MIBG uptake. However, as Dr. Y-Hassan mentions, a regional defect encompassing the akinetic region of the left ventricle is normally present. Plasma epinephrine level fluctuates and varies widely with circadian rhythm, body position, and so forth (2). In the presented study (1), the 95% confidence interval for healthy controls was 17 to 33 pg/ml for epinephrine and 488 to 989 pg/ml for norepinephrine. Of the 32 patients with Takotsubo cardiomyopathy, 4 patients had a normal plasma epinephrine level, ≤33 pg/ml, and 10 patients had a normal plasma norepinephrine level, ≤989 pg/ml. In our study, mean plasma epinephrine levels were approximately doubled in patients with Takotsubo cardiomyopathy compared to those in controls, whereas the study by Wittstein et al. (3) reported tripled levels. The absolute values of plasma epinephrine in our study were not comparable to the striking elevations reported by Wittstein et al. (3), perhaps due to the difference in methods used for catecholamine analysis. As pointed out by Dr. Y-Hassan, it remains unknown whether the observed sympathetic hyperactivity in Takotsubo cardiomyopathy is causal or secondary, but a possible causal link between catecholamine toxicity and Takotsubo cardiomyopathy has been established (4,5).

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