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Letter to the Editor

Plasma catecholamine levels in patients with takotsubo syndrome: Implications for the pathogenesis of the disease

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Takotsubo syndrome (TS) is an acute cardiac disease entity presenting with a clinical picture resembling that of acute coronary syndrome (ACS) [1–3]. The disease is characterized by a unique pattern of reversible usually regional circumferential (bi-) left ventricular wall motion abnormality (LVWMA). Invasive coronary angiography reveals no coronary culprit lesion accounting for the entire observed LVWMA. Sato and Dote introduced the term takotsubo in 1990 and 1991 to describe the angiographic silhouette of the left ventricle during systole in patients presenting with a clinical picture suggestive of myocardial infarction but with no obstructive atherosclerotic coronary artery disease [1,4]. The syndrome is frequently preceded by an emotional or a physical stress factor [5]. Previous studies have shown different results regarding the plasma level of catecholamines and their metabolites [6,7]. Despite this, it is often reported in the literature that patients with TS are associated with high levels of catecholamines. Based on these insufficient data, some researchers hypothesize that the blood borne catecholamines or high levels of plasma epinephrine alone have direct causal link to TS [8].

In this study, we report on the results of plasma levels of epinephrine, norepinephrine, and/or metanephrine and normetanephrine measurements in 33 consecutive patients with TS. These patients presented with a clinical picture resembling that of ACS and left ventricular dysfunction with a reversible circumferential pattern resulting in a conspicuous ballooning of the left ventricle during systole. Coronary angiography revealed no coronary culprit lesions accounting for the observed LVWMA. Transthoracic echocardiography was performed during admission and during follow-up to evaluate the reversibility of the LVWMA. Of all 33 patients who underwent coronary angiography, 31 patients also underwent concomitant left ventriculography; in the remaining 2 patients, the LVWMA was assessed with transthoracic echocardiography. The plasma levels of catecholamines (epinephrine and norepinephrine) and/or metanephrines (metanephrine and normetanephrine) were measured in 32 patients during the admission days (1–7 days). The majority of plasma catecholamine measurements were made during the first 48 h of admission (81% catecholamines, 68% metanephrines); during days 3–5 (15% catecholamines, 21% metanephrines); during days 6–7 (4% catecholamines, 11% metanephrines). In one patient who had pheochromocytoma, the plasma metanephrines were measured 4 months after the index presentation; this patient had 2 episodes of mid-apical TS accompanied by symptoms and signs suggestive of pheochromocytoma but the diagnosis was delayed. All plasma catecholamines and metanephrines were obtained using phlebotomy at rest in a supine position. Blood samples were placed on ice and immediately centrifuged, and the plasma was frozen. Plasma free metanephrine and normetanephrine were measured in all samples by liquid chromatography with tandem mass spectrometry, whereas their respective catecholamine precursors, epinephrine and norepinephrine were measured by high-performance liquid chromatography with electrochemical detection. The study was approved by the local institutional review board and informed consent was obtained from all patients.

Results are reported as mean ± SD except where indicated otherwise. All data analyses were done using Statistica for Windows software version 10. The Fisher exact test and chi-square test for independence were used for comparing nonparametric variables and Student's two-tailed t-test was used to compare normally distributed variables between the groups. Statistical significance was taken at a level of $p < 0.05$.

The basal characteristics of the 33 patients are shown in Table 1. The mean age of the patients was 65 years (42–82 years). The majority of the patients were females (88%) of postmenopausal age. There was evidence for a trigger factor preceding the disease onset in 88% of patients; emotional in 15 patients (45.5%) and physical in 14 patients (42.4%); in 4 patients (12%), there was no evidence of any trigger factor. Signs of heart failure developed in 9 patients (27%) including one patient who developed acute pulmonary edema. One patient with pheochromocytoma-triggered TS developed clinical signs of CT-verified ischemic stroke one week after the index presentation. Two patients died during the follow up period due to non-cardiovascular death.

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Table 1
Baselines characteristics and complications of the patients with takotsubo syndrome (n = 33).

Age (years)	65 ± 12
Female	29 (88)
Current smoking	5 (15)
Prior smoking	4 (12)
Family history of CAD	3 (9)
Treated hypertension	17 (52)
Treated hyperlipidemia	6 (18)
Diabetes mellitus	1 (3)
Time after symptom onset to coronary angiography (hours)	35.7 ± 38.1
Symptoms	
Chest pain	26 (79)
Dyspnea	9 (27)
MAP mm Hg	99 ± 18
HR beats/min	81 ± 24
ECG rhythm and changes	
Sinus	31 (94)
Atrial fibrillation	2 (6)
Suggestive of STEMI	19 (58)
Suggestive of NSTEMI	14 (42)
Cardiac biomarkers	
Troponin T (n = 28)	711 ± 1055
NT-pro-BNP (n = 25)	5567 ± 6740
Complication	
Heart failure	9 (27)
Ischemic stroke	1 (3)
Death (non-cardiovascular)	2 (6)

Data are presented as mean ± SD or absolute value (percentage).
CAD, coronary artery disease. MAP, mean arterial pressure; HR, heart rate; STEMI, ST-elevation myocardial infarction; NSTEMI, non-STEMI.

Coronary angiography was normal in 24 patients (73%); six patients (18%) had atheromatous changes with no significant obstructive coronary lesions. Three patients (9%) had coexistent obstructive coronary artery disease, which could not account for the observed LVWMA. The TS pattern was localized to the mid-ventricular region of the left ventricle in 16 patients (48.5%), mid-apical region in 14 patients (42.5%), and apical in one patient (3%): mid-basal in one patient (3%) and basal in one patient (3%).

In the 33 patients included in this study, there were available results for plasma epinephrine and norepinephrine in 27 (82%) patients and plasma metanephrine and normetanephrine in 29 (88%) patients; all 4 measurements were available in 23 (70%) patients. The measurements were made on average 1.6 days after admission for the plasma epinephrine and norepinephrine and 2.2 days for the plasma metanephrine and normetanephrine in 28 out of 29 patients. Plasma epinephrine (Normal value <0.7 nmol/L) was normal in 24 out of 27 patients (89%); was 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 one patient (3.7%). Plasma norepinephrine (Normal value: at rest 0,7-2,3 nmol/L) was normal in 14 out of 27 patients (52%), mildly elevated (1.25-fold the UNL) in 8 patients (30%) and moderately elevated (2.6-fold the UNL) in 4 patients (15%) and markedly elevated (5.6-fold the UNL) in only one patient (3.7%). Plasma metanephrine (Normal value <0.3 nmol/L) was normal in 23 out of 29 patients (79%) and mildly–moderately elevated (2.5-fold the UNL) in 5 patients (17%). Plasma normetanephrine (Normal value <0.6 nmol/L) was normal in 19 out of 29 patients (66%), mildly elevated (1.8-fold the UNL) in 9 patients (31%). In one patient with pheochromocytoma-triggered TS the plasma metanephrine and normetanephrine were as expected very high (41-fold the UNL for metanephrine and 39-fold for normetanephrine). In the 23 patients where all 4 measurements were obtained, only 2 patients (8.7%) had elevated both plasma epinephrine and metanephrine, and 6 patients (26%) had elevated both plasma norepinephrine and normetanephrine. Only 3 patients had markedly elevated catecholamine and/or their metabolite levels; one patient with pheochromocytoma-triggered mid-apical TS; one patient with ischemic stroke induced apical TS; and one patient with emotionally triggered mid-apical TS complicated by heart failure. The latter two patients had no other evidence for pheochromocytoma.

The main findings in this study are normal plasma catecholamines and their metabolites in the majority of patients with TS. The plasma epinephrine, norepinephrine, metanephrine and normetanephrine were normal in 89%, 52%, 79%, and 66% respectively. The elevation of plasma catecholamines and their metabolites in the majority of the remaining patients was mild to moderate except in 3 patients who had marked elevations: one with understandably very high levels of metanephrines because of pheochromocytoma; one with a high level of epinephrine in a patient with ischemic stroke-induced TS; and one patient with emotionally triggered mid-apical TS complicated by heart failure. Our results are in line with the findings of the majority of other albeit small studies, which have reported on the measurement of plasma catecholamines but are in contrast with the findings in the study by Wittstein et al. [6]. The latter investigators have demonstrated extremely high plasma catecholamines and their metabolites within 1–2 days of symptom onset, with marked elevations persisting for 5–7 days after the initial event.

Kurisu et al. [9] have measured plasma catecholamines in 6 patients. They found normal average circulating epinephrines, normal circulating norepinephrines in 3 patients and mild elevation in 3 patients. Ito et al. [10] have measured plasma norepinephrine in 6 patients with TS and found normal levels in one patient, mild elevation in 3 patients and marked elevation in only 2 (33.3%) patients. Akashi et al. [11] in another study reported on 10 consecutive patients with TS. They measured plasma norepinephrine on admission and found levels to be completely normal in 5 patients, mildly elevated in 3 patients and markedly elevated in 2 patients. Norepinephrine and epinephrine levels were normal in the 3 patients in whom these variables were measured in another study [12]. Yoshioka et al. [13] found no causal relationship between TS and the transient mild elevation of the catecholamines. In that study, the elevation of catecholamines was related to the severity of Killip class. Kume et al. [14] reported on increased local release of norepinephrine from the heart in 5 consecutive patients with TS. A critical review of the measurements of the plasma levels of catecholamines in the same study showed normal epinephrine levels in 3 patients, just above the normal reference value in one patient and moderate elevation in only one patient. The plasma norepinephrine was normal in 2 patients, mildly elevated in one patient and markedly elevated in only 2 out of 5 patients. Morel et al. [15] have found increased levels of plasma norepinephrine in some patients with TS but almost normal plasma epinephrine and dopamine. Madhavan et al. [7] have reported on plasma levels of free fractionated metanephrines, including metanephrine and normetanephrine in 19 patients with TS and 10 patients with STEMI. The plasma levels of fractionated metanephrine were normal in all patients in both groups. Plasma normetanephrine levels were normal in 14 (74%) of the TS patients and in 9 (90%) of the control groups with mild elevations in the remaining patients. Twenty four hour urine levels of fractionated catecholamines and metanephrines were normal in all patients with TS. The urine normetanephrine levels were mildly elevated in two patients with TS and normal in the remaining subjects. Coupez et al. [16] have recently measured the urinary metanephrine and normetanephrine in 19 patients with TS within the first 3 consecutive days after admission. The mean total, the mean urinary metanephrine and the mean urinary normetanephrine concentration were normal in the emotionally and physically triggered TS while markedly elevated in pheochromocytoma/paraganglioma induced TS.

The results in the entire group and different subgroups in the current study irrespective of the trigger factors, TS localization and different combinations of the subgroups (Table 2) are in contrast to the results of the study by Wittstein et al. However, patients with TS complicated by heart failure in the present study had significantly higher plasma normetanephrine ($p < 0.01$) and a tendency to have higher plasma metanephrine ($p = 0.08$) compared to patients without heart failure. This is in line with the study published by Yoshioka et al. [13] where