JACC: CARDIOVASCULAR IMAGING
VOL. 9, NO. 8, 2016

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcmg.2016.01.028

^{123}I-MIBG Scintigraphy in the Subacute State of Takotsubo Cardiomyopathy

Thomas Emil Christensen, MD,[a,b] Lia Evi Bang, MD, PhD,[b] Lene Holmvang, MD, DMSc,[b] Dorthe Charlotte Skovgaard, MD, PhD,[c] Ditte Bang Oturai, MS,[a] Helle Søholm, MD, PhD,[b] Jakob Hartvig Thomsen, MD,[b] Hedvig Bille Andersson, MD,[b] Adam Ali Ghotbi, MD,[a,b] Nikolaj Ihlemann, MD, PhD,[b] Andreas Kjaer, MD, DMSc,[a,c] Philip Hasbak, MD[a]

ABSTRACT

OBJECTIVES The study sought to investigate adrenergic activity in patients with takotsubo cardiomyopathy (TTC).

BACKGROUND TTC is a specific type of reversible heart failure possibly caused by excessive catecholamine stimulation of the myocardium. Scintigraphic iodine-123-*meta*-iodobenzylguanidine (*m*IBG) imaging of the heart and measurement of plasma catecholamines can be used to assess adrenergic activity in vivo. The authors hypothesized that sympathetic nerve activity is increased in the subacute state of TTC, and this study used cardiac *m*IBG imaging and plasma levels of norepinephrine and epinephrine as markers to assess this hypothesis.

METHODS In this study, 32 patients with TTC and 20 controls were examined at admission and again on follow-up with echocardiography, *m*IBG scintigraphy, and plasma catecholamine measurements.

RESULTS Ejection fraction (EF) was initially 36 ± 9% but increased to >60% ($p = 0.0004$) in all patients with TTC. In the control subjects EF was initially higher (51 ± 11%; $p = 0.0004$) than in the patients with TTC. However, EF of the patients with TTC exceeded that of the control subjects on follow-up (56 ± 8%; $p = 0.0007$). The *m*IBG imaging showed a lower late (4-h) heart-to-mediastinum ratio (H/M_{late}) (2.00 ± 0.38) and a higher washout rate (WR) (45 ± 12%) in the subacute state of TTC, both when compared with follow-up (H/M_{late}: 2.42 ± 0.45; $p = 0.0004$; WR: 33 ± 14%; $p = 0.0004$) and when compared with the control group in the subacute state (H/M_{late}: 2.34 ± 0.60, $p = 0.035$; WR: 33 ± 19%, $p = 0.026$). On follow-up, no differences in *m*IBG parameters were observed between the TTC and control groups (H/M_{late}: 2.41 ± 0.51, $p = 0.93$; WR: 30 ± 13%, $p = 0.48$) group. In the TTC group, plasma epinephrine levels were elevated in the subacute state (Log_2[epinephrine]: 6.13 ± 1.04 pg/ml), both when compared with follow-up (5.25 ± 0.62 pg/ml; $p = 0.0004$) and when compared with the control group in the subacute state (5.46 ± 0.69 pg/ml; $p = 0.044$), and these levels remained elevated in the TTC group on follow-up compared with the control group (4.56 ± 0.95 pg/ml; $p = 0.014$). No significant differences in plasma norepinephrine levels were observed.

CONCLUSIONS The present study supports a possible role of adrenergic hyperactivity in TTC. (J Am Coll Cardiol Img 2016;9:982–90) © 2016 by the American College of Cardiology Foundation.

Takotsubo cardiomyopathy (TTC) or transient left ventricular (LV) apical ballooning syndrome is an increasingly recognized cause of acute heart failure. Symptoms and signs are chest pain, dyspnea, abnormalities on the electrocardiogram (ECG), rise in cardiac biomarkers, and clinical signs of heart failure and are thus indistinguishable from the symptoms and signs of acute myocardial infarction. Because of regional wall motion abnormalities with apical and midventricular akinesia and basal

From the [a]Department of Clinical Physiology, Nuclear Medicine, and PET, Centre of Diagnostic Investigation, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [b]Department of Cardiology, The Heart Centre, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; and the [c]Cluster for Molecular Imaging, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 8, 2015; revised manuscript received December 30, 2015, accepted January 7, 2016.

hypercontractility, the left ventricle has a characteristic vase shape in end-systole that is known as apical ballooning (1,2). However, acute coronary angiography (CAG) shows no evidence of a culprit lesion. The diagnosis of TTC is usually made on the basis of the 2010 Mayo Clinic Diagnostic Criteria for Tako-Tsubo Cardiomyopathy (3).

The etiology of TTC is not yet completely understood, but several pathophysiological mechanisms have been suggested. Because the onset of TTC is often associated with emotional or physical stress (4) and given that excessive levels of both epinephrine and norepinephrine are known to have cardiotoxic effects (5), one mechanism for the development of TTC is thought to be acute hyperadrenergic myocardial stunning (6).

SEE PAGE 991

Increased myocardial sympathetic nerve activity increases exocytosis of norepinephrine from the presynaptic vesicles, and in addition terminal nerve axon reuptake of norepinephrine through the specific uptake-1 transporter is decreased (7). This process results in an increased norepinephrine concentration in the synaptic cleft. Iodine-123-*meta*-iodobenzylguanidine (*m*IBG) is a gamma-emitting norepinephrine analogue that shares the same presynaptic uptake, storage, and release mechanisms as norepinephrine, and it is used to visualize cardiac sympathetic nerve activity in vivo (8). Analysis of *m*IBG images normally includes determination of late heart-to-mediastinum ratio (H/M_{late}) and washout rate (WR). H/M_{late} offers information about global neuronal function, which is a result of norepinephrine uptake, storage, and release, and WR reflects sympathetic tone (9–11). In patients with heart failure, H/M_{late} and WR are independent predictors of prognosis and death (12–15).

Measurement of plasma epinephrine and norepinephrine is an easy and common means of assessing adrenergic drive. This method does have its limitations related to local differences in norepinephrine secretion and clearance and also because single samples do not offer an integral measure of 24-h adrenergic activity (16–18). Plasma catecholamine measurements may be useful, however, if results are interpreted with relevant caution.

AIM AND HYPOTHESIS

The aim of this study was to investigate cardiac norepinephrine activity in vivo with *m*IBG scintigraphy and plasma catecholamine levels in a large, well-characterized population of patients with TTC. Both longitudinal comparisons within the TTC group and cross-sectional comparisons with a control group were made. We hypothesized that cardiac norepinephrine activity and plasma levels of catecholamines would be increased in the subacute state of TTC compared with (A) the TTC group on follow-up and (B) the control group in the subacute state and that (C) no differences between groups would be observed on follow-up.

METHODS

Included patients were recruited at Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. The TTC group was recruited from patients admitted from December 2010 to July 2014 with suspected acute coronary syndrome (ACS), both ST-segment elevation (STE) and non-STE ACS. Study inclusion criteria were in accordance with the Mayo Clinic TTC criteria (3):

1. Acute onset of symptoms
2. No stenosis >50% of lumen diameter or evidence of a thrombus or vulnerable plaque on acute or subacute CAG
3. Typical apical ballooning on a left ventriculogram (LVG) and/or transthoracic echocardiography (TTE)
4. Elevated levels of both troponin T and creatine kinase MB
5. Normalized LV systolic function on 4-month follow-up
6. Informed patient consent to participate

An expert panel consisting of invasive, imaging, and clinical cardiology specialists reviewed acute and follow-up examinations to verify the TTC diagnosis. The control group consisted of a heterogeneous group of patients with myocarditis or aborted infarction because initial symptoms and signs closely mimicked those of TTC. Control subjects were recruited from May 2012 to February 2014 from patients admitted with suspected acute STE ACS. The inclusion criteria were as follows:

1. Admission ECG fulfilling STE ACS criteria (19)
2. No culprit lesion on acute CAG
3. Absence of typical apical ballooning on LVG and/or TTE
4. Elevated levels of both troponin T and creatine kinase MB
5. Informed patient consent to participate

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CAG = coronary angiography

ECG = electrocardiogram

H/M_{late} = late heart-to-mediastinum ratio

LV = left ventricular

LVG = left ventriculogram

***m*IBG** = iodine-123—*meta*-iodobenzylguanidine

STE = ST-segment elevation

TTC = takotsubo cardiomyopathy

TTE = transthoracic echocardiography

WR = washout rate

The study was approved by the Capital Region of Denmark Committee on Health Research Ethics (protocol #H-4-2010-054).

CAG was performed by a team of experienced interventional cardiologists. LVG was performed with automated contrast injection through a pigtail catheter in the left ventricle (iodixanol [Visipaque, GE Healthcare, Brøndby, Denmark], 16 ml/s, 55 ml total), with image recording in the right anterior oblique (30°) position. A single, experienced, blinded operator assessed end-diastolic and end-systolic volumes by planimetric tracing on the 2-dimensional images, and left ventricular ejection fraction (LVEF) was subsequently calculated (20).

TTE was done by experienced sonographers using a Philips IE33 Ultrasound System (Philips Healthcare, Eindhoven, the Netherlands) or Vivid e9 (General Electric, Oslo, Norway). Images were transferred to a remote workstation for offline analysis by Philips Xcelera analysis software version 3.1. All images were analyzed by a single investigator blinded to clinical data and angiographic results. LVEF was calculated on the basis of the wall motion score index (21), and LVEF ≥50% was considered normal (22).

The *m*IBG scintigraphy was carried out as fast as logistically possible after admission. Patients were given 130 and 20 mg potassium iodine 1 h before and 24 h after tracer injection, respectively, to block thyroid iodine uptake. Then 200 MBq of *m*IBG was injected intravenously, and planar anteroposterior images of the chest were obtained 15 and 240 min after tracer injection by using the following: a Philips Skylight gamma camera with Jetstream Software (Philips Healthcare); a medium-energy collimator; a 256 × 256 matrix; and an acquisition time of 600 s. ^{123}I was imaged with a 15% energy window set symmetrically over the 159-keV photo peak. Image interpretation was done using the Extended Brilliance Workspace NM Application Suite V4.5.3.40140 (Philips Healthcare). Images were assessed by 1 experienced observer: a region of interest was drawn above the heart by following the epicardial contour, and a rectangular region of interest was drawn above the mediastinum on early and late anterior images in accordance with published guidelines (9). Mean count within each region of interest was reported (23). For each patient H/$M_{late,}$ and WR were calculated. WR was calculated as follows:

$$WR_{BKGcorrected} = \frac{\{H_e - M_e\} - \{(H_l - M_l) \times 1.21\}}{\{H_e - M_e\}}$$

where *BKG* is background; *H* is heart mean counts per pixel; *M* is mediastinum mean counts per pixel; *e* is early; *l* is late; and *1.21* is the correction factor for ^{123}I decay at 3 h and 45 min (9).

Plasma epinephrine and norepinephrine concentrations were measured in the subacute state and at follow-up. After a 10-min supine rest, venous blood was collected in aprotinin (Trasylol) 6-ml test tubes (K2E K2EDTA Vacuette, Greiner Bio-One GmbH, Kremsmuenster, Austria). After centrifugation, plasma was stored at logged -80° C. Samples were analyzed twice by a single, experienced laboratory technician using highly sensitive enzyme-linked immunosorbent assay (ELISA) single parameter kits (Adrenaline/Noradrenaline Plasma ELISA High Sensitive, LDN Labor Diagnostika GmbH, Nordhorn, Germany) and a multimode microplate reader (FLUOstar Omega, BMG Labtech GmbH, Ortenberg, Germany). The mean value of the 2 observations was reported in picograms per milliliter.

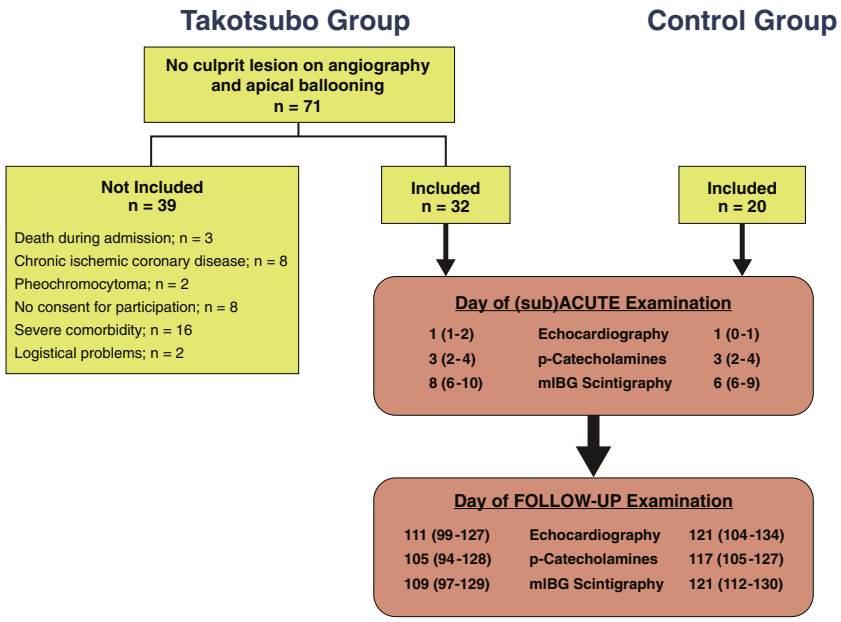
Statistical Analysis and Graphic Presentation SAS 9.4 (SAS Institute, Cary, North Carolina) software was used for statistical analysis. Normal distributed data were presented as mean ± SD unless stated otherwise, and non-normal distributed data were presented as median (interquartile range [IQR]). The skewed plasma catecholamine concentrations were $\log_2$ transformed to a normal distribution for comparison. Comparisons were made as paired or unpaired Student *t* tests as appropriate. The outcome variables were adjusted for difference in independent variables by using linear regression. All p values were corrected for multiple testing with the Benjamini-Hochberg procedure. Statistical significance for all analyses was set at $p < 0.05$. Graphic presentation was done with GraphPadPrism 6.00 (GraphPad Software, La Jolla, California).

RESULTS

This study group included 32 patients initially suspected of STE ACS (n = 25) or non-STE ACS (n = 7) and 20 patients included as controls (**Figure 1**). Initial echocardiography and *m*IBG scintigraphy were carried out as fast as logistically possible, and follow-up echocardiography and *m*IBG scintigraphy were performed within the same week approximately 4 months after admission.

PATIENT-RELATED CHARACTERISTICS. The 32 patients in the TTC group (n = 2 men, 6%) had a median age of 68 years (63 to 73 years). Twenty-two patients (69%) had experienced a physically or emotionally stressful event before admission. In 25 patients (78%), the initial ECG fulfilled conventional STE myocardial infarction criteria (19). In addition to the acute CAG, an LVG was performed in 28 patients (88%).

FIGURE 1 Study Inclusion and Examination Program



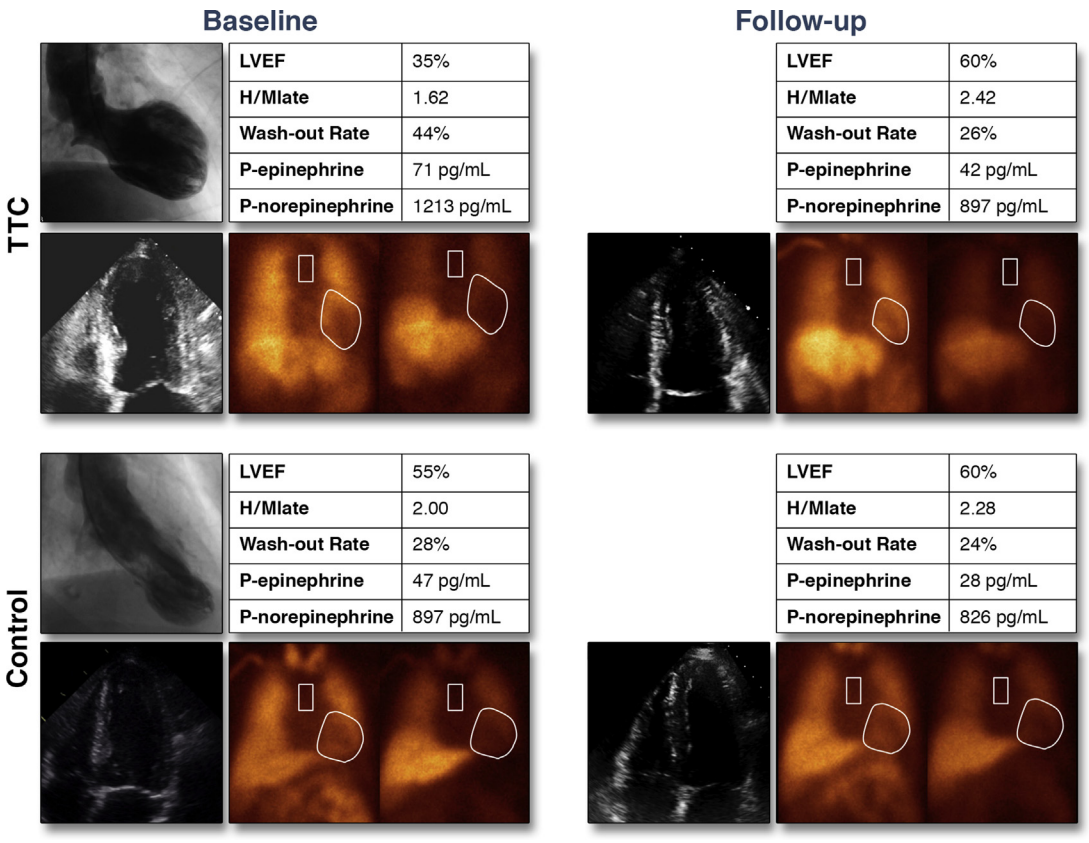
Flow chart depicts the study inclusion criteria and the examination program. *m*IBG = iodine-123–*meta*-iodobenzylguanidine; p = plasma.

The remaining 4 patients had apical ballooning confirmed by TTE. LV systolic function was impaired, planimetric LVEF was 32 ± 2%, and cardiac biomarkers were increased: troponin $T_{peak\ value}$ was 668 ng/l (IQR: 439 to 953 ng/l) (reference <50 ng/l), and creatine kinase $MB_{peak\ value}$ was 21 μg/l (IQR: 13 to 31 μg/l) (reference <4 μg/l). Compared with the TTC group, the 20 controls (n = 13 men, 65%) were generally younger, with a median age of 56 years (48 to 63 years). In addition to the acute CAG, LVGs were performed in 8 patients (40%), whereas the absence of apical ballooning was confirmed by TTE in the remaining patients. Cardiac biomarker levels were higher in the controls: troponin $T_{peak\ value}$ was 906 ng/l (range 520 to 1,810 ng/l) (reference <50 ng/l), and creatine kinase $MB_{peak\ value}$ was 44 μg/l (20 to 113 μg/l) (reference <4 μg/l) (Figure 2, Tables 1 and 2).

TRANSTHORACIC ECHOCARDIOGRAPHY. TTE was performed during admission on day 1 (IQR: 1 to 2 days) in the TTC group and on day 1 (IQR: 0 to 1 days) in the control group. In the TTC group, initial TTE showed apical ballooning and basal normokinesia or hyperkinesia. LVEF was reduced to 36 ± 9%. LVEF was initially higher in the control group (51 ± 11%; p = 0.0004). Follow-up TTE was performed 111 days (IQR: 99 to 127 days) and 121 days (IQR: 104 to 134 days) after initial admission in the TTC and control groups, respectively. In the TTC group, LVEF was >60% and LV wall motion was normal in all patients. In the control subjects, LVEF had also increased but was lower than in the patients with TTC (56 ± 8%; p = 0.0007).

IODINE-123–*META*-IODOBENZYLGUANIDINE. In the TTC group, subacute and follow-up examinations were performed 8 days (range 6 to 10 days) and 109 days (IQR: 97 to 129 days) after admission, respectively. In the control subjects, examinations were performed 6 days (IQR: 6 to 9 days) and 121 days (IQR: 112 to 130 days) after admission. In the TTC group, H/M_{late} in the subacute state was 2.00 ± 0.38. Thus, it was significantly decreased both when compared with follow-up (2.42 ± 0.45; p = 0.0004) and when compared with the control subjects in the subacute state (2.34 ± 0.60; p = 0.035). Correspondingly, WR was 45 ± 12% in the subacute state, and it was thus increased when compared with follow-up (33 ± 14%, p = 0.0004) and with the control subjects in the subacute state (33 ± 19%, p = 0.026). No difference in *m*IBG parameters was observed between the TTC and control groups on follow-up. H/M_{late} was 2.42 ± 0.45 and 2.41 ± 0.51 (p = 0.93) and WR was 33 ± 14% and 30 ± 13% (p = 0.48) in the TTC and control groups, respectively (Figure 3). We tested the null hypothesis that the difference in WR between the TTC and the control group in the acute state was independent of

FIGURE 2 Patient Examination Examples



Examples of a patient with takotsubo cardiomyopathy (TTC) and a control subject at baseline and follow-up with images of the left ventriculograms, echocardiograms, and iodine-123–*meta*-iodobenzylguanidine (*m*IBG) scintigrams, as well as data for left ventricular ejection fraction (LVEF), late heart-to-mediastinum ratio (H/M_{late}), washout rate, and plasma (p) epinephrine and norepinephrine levels.

the difference in LVEF between the 2 groups. Group and LVEF were independent variables, and WR was the dependent variable. The p value was insignificant ($p = 0.28$), and thus the null hypothesis was verified.

PLASMA CATECHOLAMINES. Blood samples for analysis of plasma epinephrine and norepinephrine were obtained 3 days (range 2 to 4 days) and 105 days (range 94 to 128 days) after admission in the TTC group and 3 days (range 2 to 4 days) and 117 days (range 105 to 127 days) after admission in the control group. In the TTC group, plasma epinephrine levels were elevated in the subacute state (Log_2[epinephrine]: 6.13 ± 1.04 pg/ml), both when compared with follow-up (Log_2[epinephrine]: 5.25 ± 0.62 pg/ml; $p = 0.0004$) and when compared with the control subjects in the subacute state (Log_2[epinephrine]: 5.46 ± 0.69 pg/ml; $p = 0.044$). In the TTC group, plasma norepinephrine levels in the subacute state (Log_2[norepinephrine]:

TABLE 1 Baseline Characteristics

	Takotsubo Cardiomyopathy (n = 32)	Control (n = 20)
Female	30 (94)	7 (35)
Male	2 (6)	13 (65)
Age, yrs	68 (63–73)	56 (48–63)
Body mass index, kg/m^2	22 (20–27)	25 (24–31)
Hypertension	14 (44)	8 (40)
Diabetes		
Non–insulin-dependent	3 (9)	1 (5)
Insulin dependent	1 (3)	0 (0)
Family history of coronary artery disease	6 (19)	5 (25)
Smoking		
Never	15 (47)	11 (55)
Previous	10 (31)	3 (15)
Active	7 (22)	6 (30)

Values are n (%) or n (interquartile range).

TABLE 2 Examination Results

	Admission			Follow-Up			
	Takotsubo Cardiomyopathy (n = 32)	Control (n = 20)	p Value	Takotsubo Cardiomyopathy (n = 32)	Control (n = 20)	p Value	p Value*
Stress exposure							
Physical	12 (38)	2 (10)		–	–		
Emotional	10 (31)	3 (15)		–	–		
Peak values of blood tests							
Troponin T <50 ng/l†	668 (439–953) ng/l	906 (520–1,810) ng/l		–	–		
Creatine kinase MB <4.0 μg/l†	21 (13–31) μg/l	44 (20–113) μg/l		–	–		
Total cholesterol <5 mmol/l†	4.9 (4.3–5.7) mmol/l	4.4 (3.6–5.1) mmol/l		–	–		
Echocardiography							
Left ventricular ejection fraction	36 ± 9%	51 ± 11%	<0.001	>60%	56 ± 8%	<0.001	<0.001
*m*IBG scintigraphy							
Late heart-to-mediastinum ratio	2.00 ± 0.38	2.34 ± 0.60	0.035	2.42 ± 0.45	2.41 ± 0.51	0.93	<0.001
Washout rate	45 ± 12%	33 ± 19%	0.026	33 ± 14%	30 ± 13%	0.48	<0.001
Plasma catecholamines							
Log_2[epinephrine]	6.13 ± 1.04 pg/ml	5.46 ± 0.69 pg/ml	0.044	5.25 ± 0.62 pg/ml	4.56 ± 0.95 pg/ml	0.014	<0.001
Log_2[norepinephrine]	10.12 ± 0.90 pg/ml	9.74 ± 0.74 pg/ml	0.24	9.89 ± 0.62 pg/ml	9.44 ± 1.00 pg/ml	0.1	0.24
[epinephrine]	70 (55-90) pg/ml	44 (35-55) pg/ml		38 (33-44) pg/ml	24 (17-33) pg/ml		
[norepinephrine]	1,113 (895-1,385) pg/ml	855 (670-1,092) pg/ml		949 (817-1,102) pg/ml	695 (488-989) pg/ml		

Values are n (%), median (interquartile range), or mean ± SD. [epinephrine] and [norepinephrine] are geometric mean with 95% confidence limits. *p values for paired comparisons between patients with takotsubo cardiomyopathy at admission and at follow-up. †Reference value.

*m*IBG = iodine-123–*meta*-iodobenzylguanidine.

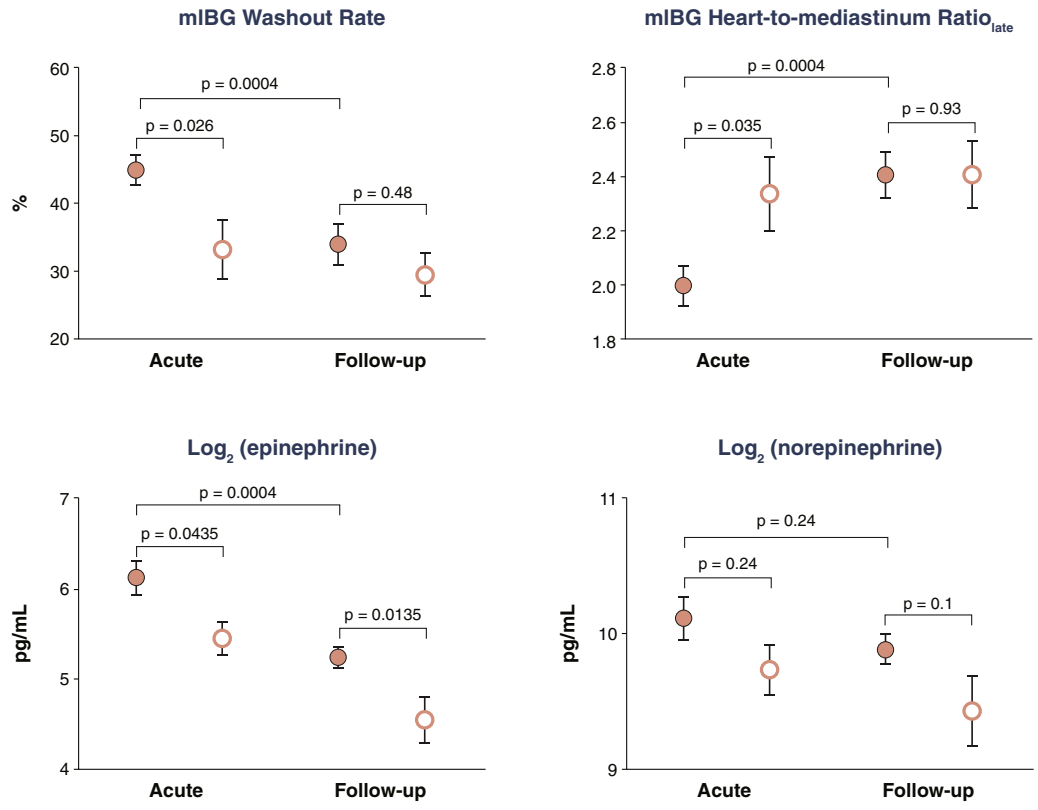
10.12 ± 0.90 pg/ml) were not different from those observed during follow-up (9.89 ± 0.62 pg/ml; p = 0.24) or in the control group in the subacute state (Log_2[norepinephrine]: 9.74 ± 0.74 pg/ml; p = 0.24). The TTC group still had increased plasma epinephrine levels (Log_2[epinephrine]: 5.25 ± 0.62 pg/ml) on follow-up when compared with the control group (Log_2[epinephrine]: 4.56 ± 0.95 pg/ml; p = 0.014). No difference was observed for norepinephrine between the TTC group (Log_2[norepinephrine]: 9.89 ± 0.62) and the control group (Log_2[norepinephrine]: 9.44 ± 0.1.00 pg/ml; p = 0.1) on follow-up (**Figure 3**, **Table 2**). The p value for the null hypothesis, that difference in plasma epinephrine between the TTC and the control groups in the acute state was independent of the difference in LVEF between the 2 groups, was insignificant (p = 0.89).

DISCUSSION

The present study prospectively evaluated cardiac norepinephrine activity with *m*IBG scintigraphy and plasma catecholamine samples in 32 patients with TTC and 20 control subjects. The most important findings were evidence of myocardial sympathetic hyperactivity and concomitantly increased plasma epinephrine in the subacute phase of TTC, both when compared with follow-up and when compared with the control group in the subacute state. On follow-up, complete remission of LV function had occurred in the TTC group, and there was no difference in *m*IBG parameters when compared with the control group. However, plasma epinephrine levels remained elevated in the TTC group. Our large study made cross-sectional comparisons of the TTC *m*IBG imaging data, and the diagnosis of TTC was established with care by thorough acute and follow-up examinations.

TTC is primarily seen in postmenopausal women (24), and it normally has a good prognosis with complete clinical remission within weeks (25). TTC is presumably caused by regional catecholaminergic stunning (26), although other mechanisms also have been suggested, including lysed infarction (27) and multivessel spasm (28). Plasma catecholamine levels have been found elevated in patients with TTC compared with patients with acute myocardial infarction and heart failure (Killip class III) (29). A suggested mechanism of the regional LV akinesia is that an excessive epinephrine level in the blood causes a switch from stimulation to inhibition of adenylate cyclase in the intracellular signaling pathway of the $ß_2$-adrenergic receptor that results in a net negative inotropic effect on the cardiomyocytes (30). In a canine model, $ß_2$-adrenergic receptor density increased from the basal toward the apical region (31), a finding that may explain why akinesia characteristically occurs in the midventricular and apical regions. Excessive norepinephrine stimulation has a cardiotoxic effect possibly mediated by the α_1-adrenergic receptor (32,33).

FIGURE 3 Graphic Presentation of *m*IBG and Plasma Catecholamine Data



Mean values with error bars depicting standard error of the mean. Closed circles represent the group with takotsubo cardiomyopathy, and open circles represent the control group. *m*IBG = iodine-123–*meta*-iodobenzylguanidine.

Abnormalities of norepinephrine activity in TTC were previously investigated, with *m*IBG imaging normally showing impaired tracer uptake in the akinetic LV region (34-36). Akashi et al. (37) examined 8 patients with TTC within the first 3 days of admission who had increased WR and decreased H/M_{late} in the acute state compared with follow-up, although the latter difference was not statistically significant. These investigators suggested a causal role of sympathetic nerve hyperactivity in TTC (37). Burgdorf et al. (38) found similar results.

Norepinephrine reuptake is blocked by high circulating levels of epinephrine (39), a finding that may account for the low H/M_{late} and high WR on *m*IBG imaging in the acute state of TTC (40). Other studies have also found abnormalities of norepinephrine metabolism that may reflect the hyperadrenergic state in TTC (29,41). The basal region of the left ventricle has a high density of sympathetic nerve endings (42), and *hyper*contractility causing LV outflow tract obstruction is occasionally present in this region (43). Thus, perhaps TTC should be thought of as 2 separate entities of heart failure with different causes: an epinephrine-induced $ß_2$-adrenergic receptor–mediated regional akinesia of the LV apex and midventricular region; and an LV outflow tract obstruction caused by norepinephrine-induced hyperkinesia of the basal region. Because it can be observed in the subacute state of TTC, sympathetic hyperactivity must be prolonged. This may have clinical implications because pharmacological reduction of the sympathetic hyperactivity may accelerate remission. Given that activation of the β_2-receptor subtype is thought to play a key role in the development of the syndrome, nonselective β-blockers may be appropriate in the treatment of TTC. TTC is associated with an anxious and worried personality type (44-46), and persons with this personality type show increased sympathetic reactivity in response to stress (47,48). The increased epinephrine level found in patients with TTC on follow-up when compared with control subjects could thus reflect a transient

hyperadrenergic state caused by the stress of re-examination.

STUDY LIMITATIONS. Our data were obtained after the onset of TTC, and *m*IBG scintigraphy was further delayed by limited tracer availability. It is therefore not possible from our results to conclude that increased adrenergic activity has a causal role in TTC. We have demonstrated only that increased cardiac norepinephrine activity is associated with the subacute state of TTC, and it could be argued that this simply represents secondary adaptation in acute heart failure. We have tried to address this issue by adjusting for the difference in LVEF between our TTC and control groups, by showing that the difference in LVEF is unlikely to account for the difference in WR. Because single photon emission computed tomography was not added, reliable predictions about regional tracer distribution in the heart cannot be made. The study was designed to yield a control group in which the disease pattern mimicked TTC as closely as possible. TTC is a syndrome diagnosis, and consequently the demarcation between it and other disease entities is blurred, posing a small risk of inclusion of atypical TTC in the control subjects.

In addition, the age and sex ratio of our prospectively included control subjects differed from that of our study group. Some studies have found no effect of age or sex on *m*IBG parameters (49), whereas others have found that older age and male sex decrease H/M_{late} and increase WR (50,51). Thus, the older age could tend to increase WR and decrease H/M_{late} in the study group, whereas the higher proportion of men could tend to increase WR and decrease H/M_{late} in the control group.

A 24-h urine collection and analysis for catecholamine metabolites demand a much more complicated setup than the convenient plasma sampling. However, such an analysis would have offered a more robust measure of overall adrenergic activity.

LVGs were performed less often in the control group. Although the relative sensitivity and specificity are unknown, baseline echocardiography is normally regarded as equal to an LVG to define apical ballooning (52).

CONCLUSIONS

In the present study, we found that *m*IBG imaging in the subacute state of TTC was characterized by decreased H/M_{late} and increased WR, as well as by increased levels of plasma catecholamines. Thus, the present study supports an assumed role of adrenergic hyperactivity in TTC.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Thomas Emil Christensen, KF 4011, Department of Clinical Physiology, Nuclear Medicine, and PET, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen E, Denmark. E-mail: Thomas.emil.christensen@regionh.dk.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The presence of adrenergic hyperactivity in the subacute state of TTC has now been documented in a large and carefully examined patient cohort.

TRANSLATIONAL OUTLOOK: That adrenergic hyperactivity plays a role in the pathogenesis of TTC may have important implications for the clinical management of such patients.

REFERENCES

1. Hurst RT, Prasad A, Askew JW III, Sengupta PP, Tajik AJ. Takotsubo cardiomyopathy: a unique cardiomyopathy with variable ventricular morphology. J Am Coll Cardiol Img 2010;3:641–9.

2. Bielecka-Dabrowa A, Mikhailidis DP, Hannam S, et al. Takotsubo cardiomyopathy: the current state of knowledge. Int J Cardiol 2010;142:120–5.

3. Madhavan M, Prasad A. Proposed Mayo Clinic criteria for the diagnosis of Tako-Tsubo cardiomyopathy and long-term prognosis. Herz 2010;35:240–3.

4. Yoshikawa T. Takotsubo cardiomyopathy, a new concept of cardiomyopathy: clinical features and pathophysiology. Int J Cardiol 2014;182C:297–303.

5. Haft JI. Cardiovascular injury induced by sympathetic catecholamines. Prog Cardiovasc Dis 1974;17:73–86.

6. Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning? Cell Mol Neurobiol 2012;32:847–57.

7. Caldwell JH, Link JM, Levy WC, Poole JE, Stratton JR. Evidence for pre- to postsynaptic mismatch of the cardiac sympathetic nervous system in ischemic congestive heart failure. J Nucl Med 2008;49:234–41.

8. Christensen TE, Kjaer A, Hasbak P. The clinical value of cardiac sympathetic imaging in heart failure. Clin Physiol Funct Imaging 2014;34:178–82.

9. Flotats A, Carrio I, Agostini D, et al. Proposal for standardization of 123I-metaiodobenzylguanidine (MIBG) cardiac sympathetic imaging by the EANM Cardiovascular Committee and the European Council of Nuclear Cardiology. Eur J Nucl Med Mol Imaging 2010;37:1802–12.

10. Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). Nucl Med Commun 1992;13:513–21.

11. Wafelman AR, Hoefnagel CA, Maes RA, Beijnen JH. Radioiodinated metaiodobenzylguanidine: a review of its biodistribution and pharmacokinetics, drug interactions, cytotoxicity and dosimetry. Eur J Nucl Med 1994;21:545–59.

12. Kioka H, Yamada T, Mine T, et al. Prediction of sudden death in patients with mild-to-moderate chronic heart failure by using cardiac iodine-123 metaiodobenzylguanidine imaging. Heart 2007;93:1213–8.

13. Nakata T, Nakajima K, Yamashina S, et al. A pooled analysis of multicenter cohort studies

of (123)I-mIBG imaging of sympathetic innervation for assessment of long-term prognosis in heart failure. J Am Coll Cardiol Img 2013;6:772–84.

14. Ogita H, Shimonagata T, Fukunami M, et al. Prognostic significance of cardiac (123)I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: a prospective study. Heart 2001;86:656–60.

15. Wakabayashi T, Nakata T, Hashimoto A, et al. Assessment of underlying etiology and cardiac sympathetic innervation to identify patients at high risk of cardiac death. J Nucl Med 2001;42:1757–67.

16. Grassi G, Mark A, Esler M. The sympathetic nervous system alterations in human hypertension. Circ Res 2015;116:976–90.

17. Wortsman J. Role of epinephrine in acute stress. Endocrinol Metab Clin North Am 2002;31:79–106.

18. van Berkel A, Lenders JW, Timmers HJ. Diagnosis of endocrine disease: biochemical diagnosis of phaeochromocytoma and paraganglioma. Eur J Endocrinol 2014;170:R109–19.

19. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

20. Kudithipudi V, Kalra N, Bhatt RD, Sorrell VL. Comparison of LVEF obtained with single-plane RAO ventriculography and echocardiography in patients with and without obstructive coronary artery disease. Echocardiography 2009;26:630–7.

21. Lavine SJ, Salacata A. Visual quantitative estimation: semiquantitative wall motion scoring and determination of ejection fraction. Echocardiography 2003;20:401–10.

22. Echocardiographic Normal Ranges Meta-analysis of the Left Heart Collaboration. Ethnic-specific normative reference values for echocardiographic LA and LV size, LV mass, and systolic function: the EchoNoRMAL study. J Am Coll Cardiol Img 2015;8:656–65.

23. Yamada T, Shimonagata T, Fukunami M, et al. Comparison of the prognostic value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: a prospective study. J Am Coll Cardiol 2003;41:231–8.

24. Kuo BT, Choubey R, Novaro GM. Reduced estrogen in menopause may predispose women to takotsubo cardiomyopathy. Gend Med 2010;7:71–7.

25. Ako J, Sudhir K, Farouque HM, Honda Y, Fitzgerald PJ. Transient left ventricular dysfunction under severe stress: brain-heart relationship revisited. Am J Med 2006;119:10–7.

26. Lyon AR, Rees PS, Prasad S, Poole-Wilson PA, Harding SE. Stress (Takotsubo) cardiomyopathy: a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. Nat Clin Pract Cardiovasc Med 2008;5:22–9.

27. Haghi D, Roehm S, Hamm K, et al. Takotsubo cardiomyopathy is not due to plaque rupture: an intravascular ultrasound study. Clin Cardiol 2010;33:307–10.

28. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M. [Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases]. J Cardiol 1991;21:203–14.

29. Wittstein IS, Thiemann DR, Lima JA, et al. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005;352:539–48.

30. Paur H, Wright PT, Sikkel MB, et al. High levels of circulating epinephrine trigger apical cardiodepression in a beta2-adrenergic receptor/Gi-dependent manner: a new model of Takotsubo cardiomyopathy. Circulation 2012;126:697–706.

31. Mori H, Ishikawa S, Kojima S, et al. Increased responsiveness of left ventricular apical myocardium to adrenergic stimuli. Cardiovasc Res 1993;27:192–8.

32. Downing SE, Lee JC. Contribution of alpha-adrenoceptor activation to the pathogenesis of norepinephrine cardiomyopathy. Circ Res 1983;52:471–8.

33. Lee JC, Sponenberg DP. Role of alpha 1-adrenoceptors in norepinephrine-induced cardiomyopathy. Am J Pathol 1985;121:316–21.

34. Cimarelli S, Sauer F, Morel O, Ohlmann P, Constantinesco A, Imperiale A. Transient left ventricular dysfunction syndrome: pathophysiological bases through nuclear medicine imaging. Int J Cardiol 2010;144:212–8.

35. Morel O, Sauer F, Imperiale A, et al. Importance of inflammation and neurohumoral activation in Takotsubo cardiomyopathy. J Card Fail 2009;15:206–13.

36. Ito K, Sugihara H, Kinoshita N, Azuma A, Matsubara H. Assessment of Takotsubo cardiomyopathy (transient left ventricular apical ballooning) using 99mTc-tetrofosmin, 123I-BMIPP, 123I-MIBG and 99mTc-PYP myocardial SPECT. Ann Nucl Med 2005;19:435–45.

37. Akashi YJ, Nakazawa K, Sakakibara M, Miyake F, Musha H, Sasaka K. 123I-MIBG myocardial scintigraphy in patients with "takotsubo" cardiomyopathy. J Nucl Med 2004;45:1121–7.

38. Burgdorf C, von Hof K, Schunkert H, Kurowski V. Regional alterations in myocardial sympathetic innervation in patients with transient left-ventricular apical ballooning (Tako-Tsubo cardiomyopathy). J Nucl Cardiol 2008;15:65–72.

39. Iversen LL. The uptake of catechol amines at high perfusion concentrations in the rat isolated heart: a novel catechol amine uptake process. Br J Pharmacol Chemother 1965;25:18–33.

40. Verschure DO, Somsen GA, van Eck-Smit BL, Knol RJ, Booij J, Verberne HJ. Tako-tsubo cardiomyopathy: how to understand possible pathophysiological mechanism and the role of (123)I-MIBG imaging. J Nucl Cardiol 2014;21:730–8.

41. Pessoa PM, Xavier SS, Lima SL, et al. Assessment of takotsubo (ampulla) cardiomyopathy using iodine-123 metaiodobenzylguanidine scintigraphy. Acta Radiol 2006;47:1029–35.

42. Kawano H, Okada R, Yano K. Histological study on the distribution of autonomic nerves in the human heart. Heart Vessels 2003;18:32–9.

43. El MR, Mansencal N, Pilliere R, et al. Prevalence and characteristics of left ventricular outflow tract obstruction in Tako-Tsubo syndrome. Am Heart J 2008;156:543–8.

44. Delmas C, Lairez O, Mulin E, et al. Anxiodepressive disorders and chronic psychological stress are associated with tako-tsubo cardiomyopathy: new physiopathological hypothesis. Circ J 2013;77:175–80.

45. Kastaun S, Schwarz NP, Juenemann M, et al. Cortisol awakening and stress response, personality and psychiatric profiles in patients with takotsubo cardiomyopathy. Heart 2014;100:1786–92.

46. Summers MR, Lennon RJ, Prasad A. Pre-morbid psychiatric and cardiovascular diseases in apical ballooning syndrome (tako-tsubo/stress-induced cardiomyopathy): potential predisposing factors? J Am Coll Cardiol 2010;55:700–1.

47. Kalk NJ, Nutt DJ, Lingford-Hughes AR. The role of central noradrenergic dysregulation in anxiety disorders: evidence from clinical studies. J Psychopharmacol 2011;25:3–16.

48. Nutt DJ. Neurobiological mechanisms in generalized anxiety disorder. J Clin Psychiatry 2001;62 Suppl 11:22–7.

49. Tsuchimochi S, Tamaki N, Tadamura E, et al. Age and gender differences in normal myocardial adrenergic neuronal function evaluated by iodine-123-MIBG imaging. J Nucl Med 1995;36:969–74.

50. Sakata K, Shirotani M, Yoshida H, Kurata C. Physiological fluctuation of the human left ventricle sympathetic nervous system assessed by iodine-123-MIBG. J Nucl Med 1998;39:1667–71.

51. Sakata K, Iida K, Mochizuki N, Ito M, Nakaya Y. Physiological changes in human cardiac sympathetic innervation and activity assessed by (123)I-metaiodobenzylguanidine (MIGB) imaging. Circ J 2009;73:310–5.

52. Templin C, Ghadri JR, Diekmann J, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. N Engl J Med 2015;373:929–38.

KEY WORDS heart failure, iodine-123-*meta*-iodobenzylguanidine scintigraphy, plasma catecholamines, takotsubo cardiomyopathy