Regional alterations in myocardial sympathetic innervation in patients with transient left-ventricular apical ballooning (Tako-Tsubo cardiomyopathy)

Christof Burgdorf, MD,[a] Katharina von Hof, MD,[b] Heribert Schunkert, MD,[a] and Volkhard Kurowski, MD[a]

Background. **Excess sympathetic nervous activity was proposed to play a crucial role in the pathogenesis of transient left-ventricular apical ballooning (TLVAB, also known as *Tako-Tsubo cardiomyopathy*). This study was conducted to assess presynaptic adrenergic alterations in the dysfunctional myocardium of patients with TLVAB.**

Methods and Results. **Ten consecutive patients undergoing coronary angiography for acute coronary syndrome who fulfilled the proposed Mayo Clinic criteria for the diagnosis of TLVAB were investigated. Myocardial iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) studies (planar and single-photon emission computed tomography [SPECT]) were performed to evaluate adrenergic innervation. Concomitantly, myocardial perfusion was assessed by means of technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) SPECT. In all patients, angiography revealed typical ballooning of the left-ventricular (LV) apex and hyperkinesis of the basal LV segments (overall ejection fraction, 41% ± 5% [mean ± SEM]). Planar ^{123}I-MIBG scans revealed decreased heart-to-mediastinum ratios at early (20 minutes) and delayed (4 hours) images (2.1 ± 0.1 and 1.9 ± 0.1, respectively). The cardiac washout rate of ^{123}I-MIBG on the late images was increased to 34% ± 3%. The ^{123}I-MIBG uptake on SPECT scans was obviously reduced in the akinetic LV apex (defect score, 3.30 ± 0.34), whereas ^{99m}Tc-MIBI SPECT indicated normal or only mildly reduced perfusion within this region (defect score, 0.89 ± 0.35).**

Conclusions. **Our study indicates a functional alteration in presynaptic sympathetic neurotransmission in patients with TLVAB, and suggests a pathophysiologic explanation of the impairment of LV function. (J Nucl Cardiol 2008;15:65-72.)**

Key Words: Apical ballooning • Tako-Tsubo • cardiomyopathy • adregenic innervation • ^{123}I-MIBG • ^{99m}TC-MIBI • SPECT

Transient left-ventricular apical ballooning (TLVAB, also known as *Tako-Tsubo cardiomyopathy*) is characterized by a reversible regional systolic dysfunction involving the apex and mid-ventricular region of the left ventricle, with hyperkinesis of the basal left-ventricular (LV) segments. Clinically, TLVAB often mimics an acute ST-segment elevation myocardial infarction, but coronary angiography reveals an absence of obstructive coronary heart disease. Several pathophysiologic mechanisms were suggested to explain TLVAB, such as multivessel coronary artery spasm, microcirculatory dysfunction, or catecholamine-induced dynamic LV outflow-tract obstruction resulting in brief ischemic periods and subsequent myocardial stunning.[1-5] Indeed, excess sympathetic nervous activity with a marked elevation of plasma catecholamine levels was found in almost 75% of the patients with TLVAB.[5] Observational data from previous case reports further indicate alterations in myocardial adrenergic neurotransmission.[6-11] However, the underlying pathophysiologic mechanism of TLVAB remains speculative.

A noninvasive and quantitative assessment of cardiac sympathetic function can be achieved by means of iodine-123 metaiodobenzylguanidine (^{123}I-MIBG), an imaging tracer that shares similar myocardial uptake, storage, and release characteristics as endogenous norepinephrine in sympathetic nerve endings.[12] Alterations in the ^{123}I-MIBG heart-to-mediastinum (H/M) ratio and cardiac washout rate were related to sympathetic denervation in the setting of LV dysfunction, associated with

From Medizinische Klinik II,[a] and Klinik für Radiologie und Nuklearmedizin,[b] Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Germany.

Received for publication May 17, 2007; final revision accepted Aug 20, 2007.

Reprint requests: Christof Burgdorf, MD, Medizinische Klinik II, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany; *christof.burgdorf@uk-sh.de.*

1071-3581/$34.00

doi:10.1016/j.nuclcard.2007.08.005

several forms of cardiomyopathy and myocardial infarction, respectively.[13-17]

In an attempt to define putative alterations in the cardiac sympathetic nervous system, we investigated the H/M ratio and washout rate as well as regional myocardial defects of ^{123}I-MIBG uptake in patients with TLVAB. In addition, technetium-99m methoxyisobutylisonitrile (^{99m}Tc-MIBI) single-photon emission computed tomography (SPECT) was performed to evaluate possible defects of myocardial perfusion in this newly recognized cardiomyopathy.

METHODS

Ten consecutive patients undergoing coronary angiography for acute coronary syndrome who fulfilled the proposed Mayo Clinic criteria for the diagnosis of TLVAB[2] were investigated. Left ventriculography and multiplane coronary angiography were performed within 3 to 32 hours after the onset of clinical symptoms by the femoral approach, using standard techniques. The overall LV ejection fraction was calculated from a planimetric evaluation of end-diastolic and end-systolic volume in the 30° right anterior oblique projection. Obstructive coronary heart disease was defined as >50% reduction in the lumen diameter of the major epicardial coronary artery. Each patient underwent 12-lead electrocardiography and serial measurements of creatine kinase, creatine kinase muscle-brain (MB) fraction, and troponin T. The assessment of plasma catecholamines was performed in 7 patients on hospital day 1. Two-dimensional transthoracic echocardiography was performed within 24 hours after hospital admission, and again between hospital days 3 to 10. Echocardiographic estimation of the LV ejection fraction was performed in the four-chamber view, according to the method of Simpson.

Myocardial ^{123}I-MIBG studies were performed between hospitals day 3 to 9. Each patient received an intravenous injection of 200 MBq of ^{123}I-MIBG at rest. Planar imaging and SPECT imaging were performed 20 minutes and 4 hours after administration of ^{123}I-MIBG by means of a triple-head gamma camera (3000XP, Marconi/Philips, Hamburg, Germany) with the following specifications: for planar imaging, 10 minutes/frame, matrix 512 × 512, zoom 1.3; and for SPECT imaging, 120°, 6°/step, 60 sec/step, 128 × 128 matrix, iterative reconstruction. To determine the H/M ratio and cardiac washout rate, regions of interests were drawn manually and analyzed semiquantitatively. The ^{123}I-MIBG washout rate was defined as percent changes in cardiac activity (H) from early (20 minutes) to delayed (4 hours) images: $(H_{early} - H_{delayed})/(H_{early})$, after decay correction. The ^{99m}Tc-MIBI SPECT was performed 1 day after ^{123}I-MIBG studies were performed. Each patient received an intravenous injection of 440 MBq of ^{99m}Tc-MIBI 2 hours before SPECT imaging. A triple-head gamma camera (3000XP, Marconi/Philips) was used with the following specifications: 120°, 6°/step, 50 seconds/step, 128 × 128 matrix, iterative reconstruction, and filtered back projection (low pass).

Table 1. Patient characteristics (n = 10)

Age (y)	67 ± 4
Female gender (n)	9
Body mass index (kg/m^2)	23 ± 1
Mean arterial blood pressure (mm Hg)	94 ± 5
Peak troponin T (μg/L)	0.74 ± 0.23 (normal, <0.1 μg/L)
Peak creatine kinase (U/L)	308 ± 91 (normal, <140 U/L)
Peak creatine kinase MB (U/L)	34 ± 6 (normal, <23 U/L)
Plasma norepinephrine (ng/L)	735 ± 231 (normal, <420 ng/L)
Plasma epinephrine (ng/L)	153 ± 69 (normal, <84 ng/L)
Risk factors	
Arterial hypertension (n)	7
Hypercholesterolemia (n)	3
Diabetes mellitus (n)	1
Current smoker (n)	1

Data are present as mean ± SEM.
MB, muscle-brain.

The SPECT images of the left ventricle were divided into 17 semiquantifiable segments for assessment of the regional defect score according to the recommendations of the American Heart Association Writing Group on Myocardial Segmentation and Registration for Cardiac Imaging.[18] Each segment was visually graded by assigning scores between 0 and 4 (0 = normal tracer uptake, 1 = mildly reduced tracer uptake, 2 = moderately reduced tracer uptake, 3 = obviously reduced tracer uptake, and 4 = absent tracer uptake). All scans were analyzed by an experienced nuclear cardiologist blind to all clinical variables of patients.

Data are given as means ± SEM. Statistical analyses were performed with the two-tailed paired Student *t* test when two parameters were compared (echocardiographic LV ejection fraction on hospital admission and during follow-up, and ^{123}I-MIBG H/M ratio for early and delayed images). One-way analysis of variance combined with the Bonferroni post hoc test was used to assess differences between ≥3 parameters (segmental LV defect scores). Correlation coefficients were determined and evaluated by the Pearson test. Multiple linear regression analysis was performed using the early and delayed ^{123}I-MIBG H/M ratios as dependent parameters. Plasma norepinephrine and epinephrine, peak creatine kinase, creatine kinase MB fraction, and troponin T were used as independent parameters. The partial regression coefficient (β) was calculated to evaluate significant independent parameters. A value of $P < .05$ was considered statistically significant.