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Abnormal coronary vasoreactivity in transient left ventricular apical ballooning (tako-tsubo) syndrome

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ABSTRACT

Background: The exact etiology and pathophysiologic mechanisms of tako-tsubo syndrome (TTS) remain controversial.
Objective: To further evaluate the abnormal coronary vasoreactivity and its possible anatomical substrate in TTS.
Methods: We studied 47 patients (46 women; age 67 ± 12 years) who underwent diagnostic cardiac catheterization and evaluation of coronary vasoreactivity by sequential acetylcholine (Ach), nitroglycerine and adenosine testing with angiographic and intracoronary pressure-Doppler flow monitoring. Coronary artery wall morphology was also evaluated by intravascular ultrasound (IVUS) imaging in 45 vessels of 43 patients.
Results: Abnormal coronary vasoconstriction to Ach stimulation was elicited in 40 patients (85%) involving the LAD artery and its branches in 39 (83%). Abnormal microvascular function was seen in 39 (83%) patients. Overall, hyperemic microvascular resistance index (HMR) was higher and Doppler coronary flow velocity reserve (CFVR) was lower in the LAD artery territory as compared to the reference territories (2.64 ± 1.23 vs 2.05 ± 0.56; $p = 0.008$ and 1.95 ± 0.7 vs 2.3 ± 0.6; $p = 0.018$, respectively). IVUS revealed no plaque rupture, dissection or thrombosis but occult plaque formation and myocardial bridging were found as a possible anatomical substrate of endothelial dysfunction in 67% and 48.8% patients respectively.
Conclusions: A global failure of coronary vasomotor function was demonstrated in most TTS patients. These findings implicate abnormal vasoconstrictive response to the activation of the sympathetic system as a potential mechanism involved in the pathogenesis of myocardial stunning in TTS.
Perspectives: **Competency in medical knowledge**: Abnormal coronary vasoconstriction secondary to endothelial dysfunction may actively contribute to the clinical manifestation of acute coronary syndromes in patients with non-obstructive coronary disease.
Translational outlook 1: TTS patients reveal a global failure of vasomotor function with both vasoconstrictive response to acetylcholine and increased hyperemic microvascular resistances in the territory of myocardial stunning. They may also show occult coronary atherosclerosis and myocardial bridging as the anatomic substrates of endothelial dysfunction.
Translational outlook 2: The cardiac phenotype of TTS includes a high prevalence of coronary vasomotor disturbances. These findings implicate abnormal vasoconstrictive response to the activation of the sympathetic system as a potential mechanism involved in the pathogenesis of TTS in post-menopausal women. Thus, a systematic evaluation of coronary vasoreactivity could better characterize the syndrome.

1. Background and purpose of the study

In spite of the large number of case reports, clinical studies and review articles published since the first description by Sato et al. [1] in 1990, the exact pathophysiologic mechanisms of transient left ventricular apical ballooning, also termed stress cardiomyopathy, tako-tsubo cardiomyopathy or tako-tsubo syndrome (TTS) [1–7], has not been fully elucidated and remains the subject of debate.

Disparate possible mechanisms have been proposed, including simultaneous multivessel coronary artery vasoconstriction [1,2,8,9], primary microcirculatory dysfunction [10–13], direct myocyte catecholamine injury, [14–17] or aborted acute myocardial infarction secondary to transient coronary occlusion by a fast-dissolving clot from an ulcerated plaque undetected by coronary angiography [18,19].

Multivessel epicardial coronary artery spasm has been suggested as a possible cause of post-ischemic stunning since the early descriptions

Abbreviation: TTS, tako-tsubo syndrome; Ach, acetylcholine; NTG, nitroglycerine; Ado, adenosine; LAD, left anterior descending; IVUS, intra-vascular ultrasound imaging; QCA, quantitative coronary angiography; APV, average peak velocity; CFVR, coronary flow velocity reserve; HMR, hyperemic microvascular resistance; LA, lumen area; VA, vessel area; PA, plaque area; RPA, relative plaque area; OCT, optical coherence tomography.

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of the syndrome [1–3]. However, spontaneous spasm has been demonstrated in few reports and vasomotor dysfunction testing has not been actively investigated in most series of patients. The aim of our study was to further evaluate abnormal coronary vasoreactivity and its possible anatomical substrate in TTS.

2. Patients and methods

2.1. Patients

Among 5620 patients undergoing cardiac catheterization for acute coronary syndrome between May 2007 and May 2015, 74 patients fulfilled the diagnostic criteria of TTS (1.3%). The clinical diagnosis of TTS was made in the presence of 1) chest pain with new ischemic ECG changes 2) transient and severe left ventricular regional wall-motion abnormalities, 3) modest elevation in cardiac troponin levels as compared to the extent of wall motion abnormalities, 4) absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture, 5) absence of myocarditis, new electrocardiographic Q-wave or evidence of myocardial scar and 6) recovery of ventricular systolic function within days or weeks [1–7]. Twenty-seven patients were excluded because of unstable conditions, inability to withdraw vasoactive medication, late presentation, or refusal to give informed consent to the study protocol. Thus, the study population consisted of 47 TTS patients (46 women; age 67 ± 12 years) who underwent cardiac catheterization within 3.5 ± 4.7 days (range: 1–15, median: 2.0 days) from symptoms onset. Patient's clinical and angiographic characteristics are summarized in Table 1.

2.2. Study protocol

Coronary vasomotor function was evaluated immediately after the diagnostic coronary angiography or a few days later to allow the withdrawal of vasoactive medications (nitrates, calcium antagonists, ACE-inhibitors). Antiplatelet therapy, beta-blocking agents and statins were usually allowed. Informed consent to the full study was obtained from all patients according to the clinical protocol of drug evaluation of coronary vasomotor function approved by the local ethical committee and to the ethical guidelines of the 1975 Declaration of Helsinki. After administration of body weight adjusted heparin (60 UI/kg) a 0.014″ floppy intracoronary Doppler Flow-wire™ (33 patients) or a dual pressure and flow sensor Combo-wire™ (14 patients) connected with a dedicated instrument (Flowire System Volcano, Rancho Cordova, CA) were used to record coronary pressure and flow velocities. The wire was advanced through a 6F guiding catheter into the left anterior descending (LAD) artery and manipulated to obtain the best fitting of the Doppler flow spectrum. Epicardial endothelium-dependent coronary vasomotor function was studied first, followed by assessment of microvascular vasodilator capacity as detailed hereafter.

Table 1
Patients clinical and angiographic characteristics.

Number of patients	47
Age (years)	67 ± 12
Women (%)	46 (98%)
Hypertension	30 (64%)
Diabetes	5 (11%)
Hyperlipidemia	20 (43%)
Smoking	8 (17%)
Emotional or physical stress trigger	36 (77%)
Mean peak CK (UI/L)	225.3 ± 138.5
Mean peak TnI (μg/dL)	2.88 ± 2.5
Non-significant CAD	16 (30%)
Wrap-around apical LAD	34 (72%)
Intramyocardial LAD path	21 (48.8%)
LVEF (%) on admission	46 ± 8%
Apical ballooning type	45 (95.7%)
Mid-ventricular type	2 (4.2%)

Then, coronary intravascular ultrasound imaging (IVUS) was performed by manual pullback of the imaging catheter over the same wire. Finally, the flow-wire was withdrawn from the LAD artery and advanced into the left circumflex (35 patients) or the right coronary artery (6 patients). Coronary pressure and flow velocities were recorded again to evaluate microvascular vasodilator capacity and microvascular resistance indexes of a "non-LAD" territory. Recovery of left ventricular function was evaluated by repeated transthoracic echocardiography during index hospitalization and follow-up (30.8 ± 12.1 days).

2.3. Epicardial coronary function

Endothelium-dependent coronary vasodilatation was studied by 3-minute infusion of increasing doses (10–7 mol/L, 10–6 mol/L and 10–5 mol/L or 0.72 μg/min, 7.2 μg/min and 36 μg/min) of intracoronary acetylcholine (Ach) (Miovisin, Farmigea SpA, Pisa, Italy). Ach was administered through the guiding catheter into the left main using a syringe pump (Alaris GP Volumetric pump Care-Fusion-Switzerland) with continuous monitoring of intracoronary Doppler flow velocity, blood pressure and electrocardiogram. Ach testing was repeated into the right coronary artery only in two patients. Two-view angiography quantitative coronary analysis (QCA) was performed at each step using the Philips QCA analysis system and the percent change in lumen diameter of major epicardial coronary vessels was measured. Drug infusion was stopped at the end of the high dose administration or at any time due to occurrence of severe chest pain, significant coronary vasoconstriction and abrupt drop of coronary blood flow velocity, atrial standstill or atrial-ventricular (A-V) block. We did not routinely insert a temporary right ventricular pacing electrode into the right ventricle during testing. The normal response to Ach is vasodilation of the epicardial vessels. Epicardial endothelium-dependent coronary vasomotor dysfunction was defined as >50% reduction in coronary diameter at peak Ach infusion [20–22]. At the end of Ach testing, the non-endothelium dependent relaxation of the epicardial vessels was assessed by QCA after intracoronary nitroglycerine (NTG) administration (250 mcg). Abnormal epicardial non-endothelium dependent vasodilatation was defined as <5% increase from the baseline lumen diameter after NTG.

2.4. Microvascular coronary function

The microvascular vasodilator function was studied after Ach testing and intracoronary NTG administration to abolish epicardial artery vasomotor tone. The microvascular vasodilator function was evaluated by assessing coronary blood flow response to intracoronary administration of 100–300 μg of adenosine (Ado, Krenosin, Sanofi-Winthrop). The ratio of hyperemic and baseline intracoronary Doppler average peak velocity (APV) was used to measure the coronary flow velocity reserve (CFVR) and relative flow reserve (RCFR) as previously described [23,24]. Microvascular dysfunction was defined as a CFVR < 2.5. The ratio of mean coronary pressure and APV at peak hyperemia was measured to determine the microvascular hyperemic resistance indexes (HMR). Abnormal microvascular resistances were defined as HMR > 2.0 [25].

2.5. Intravascular ultrasound imaging

IVUS imaging was performed using a 30 mHz phase array ultrasound catheters (Aigle Endosonics, Volcano Inc., Rancho Cordova, CA) connected with the integrated Volcano imaging system (Volcano Inc., Rancho Cordova, CA). Cross sectional 2D reconstruction grey-scale and ECG-gated frequency domain images were obtained during continuous manual pullback of the imaging catheter from the distal to the proximal sections of the vessel under fluoroscopic guidance. Atherosclerotic changes of the arterial wall, significant plaque formation and intimal thickening as well as plaque rupture, thrombosis and dissection were defined according to the guidelines for classification and analysis of