Reversible impairment of coronary flow reserve in takotsubo cardiomyopathy: A myocardial PET study

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Background. **The precise etiology of takotsubo cardiomyopathy remains unclear. The study of myocardial blood flow (MBF) and coronary flow reserve (CFR) by use of positron emission tomography might help in understanding this syndrome.**

Methods and Results. **Three postmenopausal women underwent adenosine/rest perfusion with nitrogen 13 ammonia and metabolism with fluorine 18 fluorodeoxyglucose positron emission tomography, coronary angiography, cardiac magnetic resonance, and echocardiography in the acute phase of takotsubo cardiomyopathy and at 3 months' follow-up, after normalization of left ventricular function. PET study was performed in 2 parts: the perfusion analysis with nitrogen ammonia and the metabolism of the heart using FDG. MBF and CFR were analyzed quantitatively in the acute phase and at follow-up. The images highlighted the impairment of tissue metabolism in the dysfunctioning left ventricular segments in the acute phase, mainly in the apical segments and progressively less in the medium segments. At the same time, a clear inverse metabolic/perfusion mismatch emerged, which normalized 3 months later. The quantitative analysis of MBF showed a reduction in the acute phase in apical segments in comparison to basal segments without differences between midventricular and basal segments. In the acute phase CFR proved to be reduced in apical versus basal segments. CFR impairment of apical segments recovered completely after 3 months.**

Conclusion. **The acute phase of takotsubo cardiomyopathy is characterized by an inverse perfusion/metabolism mismatch with a reduction in CFR in the apical segments. However, the impairment of CFR and the reduction of metabolism in the apical segments recovered completely after 3 months. (J Nucl Cardiol 2008;15:811-7.)**

Key Words: Apical ballooning syndrome • takotsubo cardiomyopathy • coronary flow reserve • positron emission tomography

Takotsubo cardiomyopathy, also called transient left ventricular (LV) apical ballooning syndrome, is a rare form of transient LV dysfunction that mimics an acute coronary syndrome,[1,2] characterized by hypokinesis and dyskinesis of the apical segments and hypercontractility of the basal segments, in total absence of atherothrombotic coronary artery disease. This acute cardiac syndrome was first described in the Japanese population,[3] and although it is being reported more frequently, the exact cause of the syndrome and its physiopathology remain unknown.

Dynamic positron emission tomography (PET) with nitrogen 13 ammonia and tracer kinetic modeling has been used intensively in the past for the noninvasive measurement of myocardial blood flow (MBF) and coronary flow reserve (CFR) in patients with cardiac disorders.[4-10] The absolute quantitation of regional MBF is used for the evaluation of the severity of coronary obstructions and for decision making regarding the need for coronary revascularization. PET with fluorine 18 fluorodeoxyglucose (FDG) is used as an indicator of myocardial metabolism.[11]

In the acute phase this syndrome presents as a transient metabolic disorder at the cellular level, which was recently demonstrated by evidence of the impairment of tissue metabolism in the dysfunctioning left ventricle with preserved MBF at rest.[12,13]

The aim of this observational study was (1) to analyze changes in MBF and CFR in the acute phase of

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takotsubo cardiomyopathy and at follow-up and (2) to investigate whether the flow/metabolism mismatch pattern observed with PET imaging is reversible or permanent.

METHODS

Patients

All patients underwent coronary angiography, transthoracic echocardiography, myocardial PET and cardiac magnetic resonance imaging (MRI) in the acute phase. Except for coronary angiography, all of the noninvasive studies were repeated at 90 days after hospital discharge to evaluate eventual changes from baseline. Takotsubo cardiomyopathy was defined as a syndrome characterized by transient LV dysfunction, electrocardiographic changes and acute onset of chest pain that can mimic acute myocardial infarction, and minimal release of myocardial enzymes in the absence of obstructive coronary artery disease. All of these conditions were necessary to confirm the diagnosis.

Coronary Angiography

Selective coronary angiography was performed via the Judkins technique within 1 hour of hospital admission. An experienced angiographer assessed the degree of coronary stenosis. For the purpose of the study, a coronary stenosis greater than 50% on quantitative coronary analysis was considered significant.

Echocardiography

Resting transthoracic echocardiograms were obtained in all patients immediately after coronary angiography. Examinations were performed with a wide-angle mechanical scanner (2.5-MHz Sonos 5500; Hewlett-Packard, Palo Alto, Calif). Two-dimensional apical 2- and 4-chamber views were used for ventricular volume measurements. Left ventricular ejection fraction (LVEF) was calculated via a modified Simpson's method by use of biplane apical (2- and 4-chamber) views. Echocardiography was performed by experienced cardiologists blinded to the results of myocardial PET with an intraobserver variability in LVEF of less than 5%.

Positron Emission Tomography

The PET examinations were performed within three days after admission. On 2 consecutive days, 3 PET investigations were performed on each patient including FDG for viability testing and ammonia in both baseline and hyperemic conditions for perfusion. All scans were carried out with the Discovery LS PET/computed tomography (CT) hybrid system (GE Healthcare, Waukesha, Wis). Every PET study was preceded by a CT scan for attenuation correction. To reduce artifacts due to heart movement and breathing, a slow CT helical scan was used that entailed 27.5 seconds to acquire the whole heart field of view. Furthermore, CT and PET images were visually checked for potential misregistration. All PET studies were performed in 2-dimensional mode for scatter reduction. Images were reconstructed with an ordered-subset expectation maximization 28-subset 3-iteration algorithm with an in-plane image resolution of 4.8-mm full width at half maximum. The reconstruction matrix was 128 × 128 pixels with a 3.9-mm pixel size.

Determination of CFR

On day 1, PET ammonia studies were carried out under rest and hyperemic conditions. PET dynamic acquisition (12 × 10 seconds, 4 × 30 seconds, and 1 × 360 seconds) was started immediately after injection of 550 to 590 MBq of ammonia. Pharmacologic stress testing was performed with an adenosine infusion at 140 $\mu g \cdot kg^{-1} \cdot min^{-1}$ over a period of 6 minutes, starting 3 minutes before and ending 3 minutes after ammonia administration.

FDG PET

On day 2, after fasting for 12 hours, patients were injected with 378 to 402 MBq of FDG, and CT acquisition was started 1 hour later. The injection of tracers was preceded by a short hyperinsulinemic-euglycemic clamp that obtained a similar metabolic milieu. (For the first scan, at baseline, the mean glycemic level was 85 mg/dL and mean insulin level was 3.5 U/L; after FDG injection, the mean glycemic level was 68 mg/dL and the mean insulin level was 44 U/L. For the follow-up scan, at baseline, the mean glycemic level was 106 mg/dL and the mean insulin level was 4.7 U/L; after FDG injection, the mean glycemic level was 73 mg/dL and the mean insulin level was 69.4 U/L.) A standard protocol for the hyperinsulinemic-euglycemic clamp was used.[14] After an overnight fast, a 20-gauge polyethylene cannula was inserted into a superficial forearm vein for insulin and 20% glucose solution infusion. A second cannula was placed in the other arm after being "arterialized" by heating with an external lamp to a temperature of 45°C to 50°C. Before the insulin clamp was started, the doses of glucose (via a dry chemistry enzymatic method) and insulin (via an immunofluorometric assay [AIA 21 system; Eurogenetics-Tosoh, Saran, France]) (normal range, 4-20 mU/L) were obtained. Approximately 60 minutes before the F-18 FDG injection, a constant insulin infusion at a dose of 40 $mU \cdot min^{-1} \cdot m^{-2}$ of body surface area was performed. "Arterial" blood glucose levels were monitored at 5-minute intervals from the contralateral arm. Glucose infusion was started after 4 minutes of insulin infusion, and the rate was adjusted to maintain baseline glucose levels.[9] Steady state was defined as 3 consecutive blood glucose values within ± 5%. When this condition was obtained, F-18 FDG was injected, and the clamp was maintained for the duration of the PET acquisition.

Tracer Kinetic Analysis

The reconstructed axial images of all frames were reoriented into short-axis views of the left ventricle. The reorientation parameters were defined on the last frame of the acquisi-