Metabolic evidence of myocardial stunning in takotsubo cardiomyopathy: A positron emission tomography study

Kotaro Obunai, MD, Deepika Misra, MD, Andrew Van Tosh, MD, and Steven R. Bergmann, MD, PhD

Several case studies of acute transient left ventricular apical ballooning without significant coronary artery disease (takotsubo cardiomyopathy) have been reported.[1-5] The pathophysiologic mechanism of this syndrome is believed to be related to catecholamine-induced stunning of the apical myocardium. Definitive proof, however, is lacking.

Here we report a case of transient apical ballooning in which metabolic imaging with positron emission tomography (PET) revealed profoundly reduced fluorine-18 fluorodeoxyglucose (FDG) uptake in the ballooned apical wall with relatively normal perfusion, a pattern consistent with myocardial stunning. This perfusion-metabolism pattern normalized, as did contractility.

Case report. A 52-year-old white woman presented to the emergency department 8 hours after the acute onset of chest pain and shortness of breath. Symptoms started and then waxed and waned after an emotional argument with her husband. She denied tobacco, alcohol, or drug use. Her past medical history was only significant for hyperlipidemia, for which she had been taking atorvastatin. On arrival, her blood pressure was 77/50 mm Hg and her heart rate was 88 beats/min. Jugular venous distension was appreciated in the sitting position, and respiratory crackles were heard bilaterally. No murmurs, rubs, or gallops were appreciated. The electrocardiogram revealed mild ST elevation in leads II, III, and aVF with diffuse T-wave inversion and QT prolongation (Figure 1). A chest radiograph was consistent with bilateral pulmonary parenchymal congestion. Emergent coronary angiography revealed normal coronary arteries. Left ventriculography showed distal anterior, apical, and distal inferior akinesis with hyperkinesis of the remaining walls (Figure 2). The level of serum troponin I was mildly elevated at 0.64 ng/mL. In the acute phase, the patient displayed hemodynamic instability, requiring intraaortic balloon counter pulsation to maintain adequate perfusion. Over the next 3 days, she showed a marked clinical improvement with resolution of heart failure. On hospital day 6, she underwent PET scanning with rubidium-82 to assess resting perfusion and with F-18 FDG, after oral glucose loading, to assess metabolism.

Perfusion imaging revealed a moderate perfusion defect involving the distal anterior and apical wall. Metabolic imaging revealed severely reduced F-18 FDG uptake in a large area of the mid to distal anterior, anteroseptal, apical, and inferoapical walls (Figure 3). The extent of the metabolic defect was much larger and more severe than the perfusion abnormality. The patient was discharged on hospital day 8 on medical therapy. Echocardiography was repeated 3 months later and showed normalization of left ventricular wall motion. Repeat PET imaging revealed marked improvement of myocardial F-18 FDG uptake in the anteroapical and inferoapical walls (Figure 3).

Discussion. To our knowledge, this is the first case report of acute transient apical ballooning without coronary artery stenosis, so-called takotsubo cardiomyopathy, in which acute and follow-up evaluation of the myocardial metabolism by use of PET was performed.

Takotsubo cardiomyopathy is characterized by (1) a reversible balloon-like left ventricular apical wall motion abnormality with hypercontraction of the basal segments, (2) chest pain and ST-T–segment abnormalities on the electrocardiogram mimicking acute myocardial infarction, (3) minimal evidence of epicardial coronary artery stenosis, (4) induction by physical and emotional stress, and (5) a favorable prognosis.[6] Because this apical wall motion abnormality has been demonstrated to be reversible clinically, focal stunning of the myocardium has been proposed as the underlying condition in this disorder.[4,5] However, there is little pathophysiologic evidence to support this claim.

Braunwald and Kloner[7] originally described stunned myocardium as "prolonged, postischemic dysfunction of viable tissue salvaged by reperfusion." This phenomenon

From the Division of Cardiology, Beth Israel Medical Center, New York, NY.

Reprint requests: Steven R. Bergmann, MD, PhD, Chief of Cardiology, Beth Israel Medical Center, First Avenue at 16th Street, Baird Hall 5th Floor, New York, NY 10003; *sbergmann@bethisraelny.org.*

J Nucl Cardiol 2005;12:742-4.

1071-3581/$30.00

doi:10.1016/j.nuclcard.2005.06.087

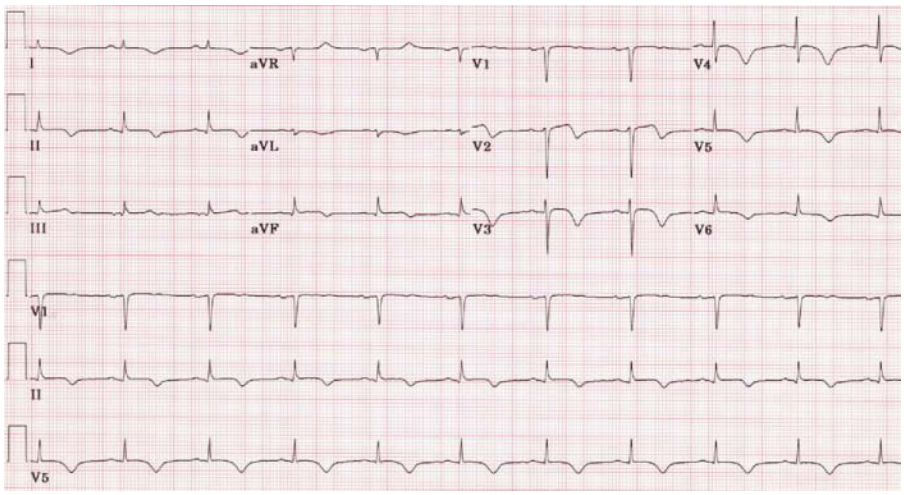

Figure 1. Electrocardiogram on presentation to emergency department demonstrating mild ST elevation in leads II, III, and aVF with diffuse T-wave inversion and QT prolongation.

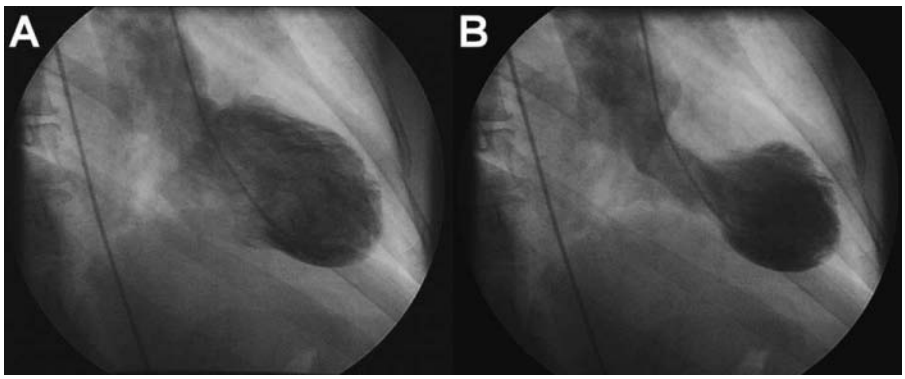

Figure 2. Left ventriculogram during diastole (**A**) and systole (**B**) showing distal anterior, apical, and distal inferior akinesis with hyperkinesis of the remaining walls.

is thought to be a form of reperfusion injury.[8] Metabolic changes in stunned myocardium, including alterations in glucose and fatty acid uptake, have been studied.[9-14] Transiently reduced glucose utilization, despite normal perfusion, is considered by multiple investigators as the metabolic state of stunned myocardium. In an experimental dog model, Di Carli et al[12] showed a prolonged reduction of F-18 FDG uptake in stunned myocardium subjected to multiple cycles of ischemia and reperfusion—so-called repetitive stunning. Perrone-Filardi et al[13] first described reverse perfusion-glucose metabolism mismatch (reduced F-18 FDG uptake with relatively normal resting blood flow) in patients with repetitive stunning. The precise mechanism for this reduced glucose uptake in stunned myocardium remains unknown. One possible explanation may be that shifting levels of metabolites after ischemia and reperfusion may decrease the activity of key regulatory enzymes of the glycolytic pathway.[15] Another possibility is that reduced sensitivity to calcium in stunned myocardium may inhibit translocation of glucose transporter-4 from an intracellular pool to the sarcolemma, thus decreasing glucose uptake.[16]

Radionuclide imaging has been playing an important role in understanding the underlying pathophysiology of takotsubo cardiomyopathy. Although there is no consensus as to the mechanism responsible for apical ballooning, catecholamine toxicity due to intense activation of the sympathetic nervous system has been proposed as the most likely cause of myocardial stunning in this syndrome.[4-6] Owa et al[17] studied 4 patients with apical ballooning using iodine 123 metaiodobenzylguanidine (MIBG), I-123 β-methyl-iodophenyl-pentadecanoic acid (BMIPP), and thallium 201 and found that MIBG had the highest defect scores, suggesting that the disturbance of the sympathetic innervation and catecholamine-mediated myocardial injury may be central in this disorder.

To date, only a few studies evaluating the metabolic changes in takotsubo cardiomyopathy have been re-

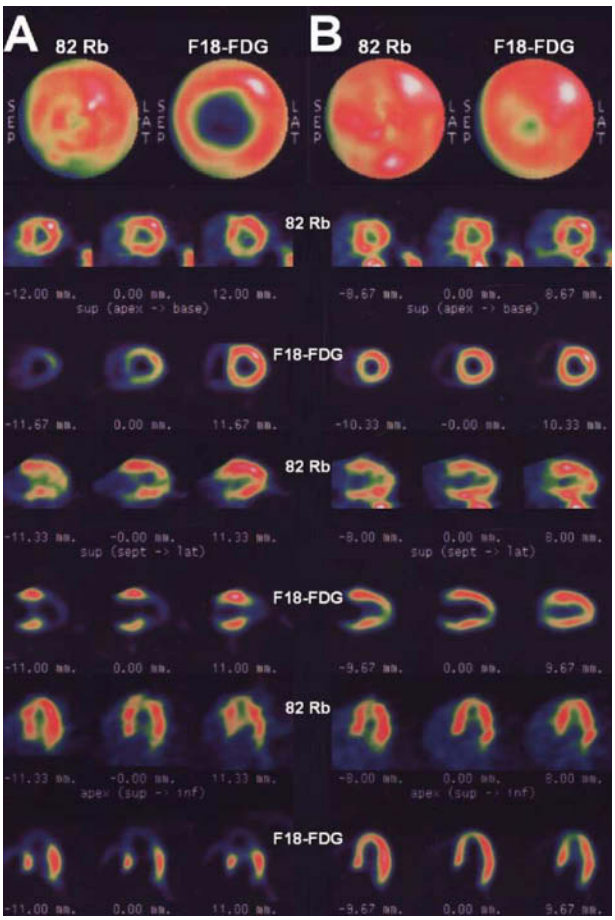

Figure 3. A, Myocardial PET images on hospital day 6 showing moderate perfusion defect involving distal anterior and apical wall. Metabolic images revealed severely reduced F-18 FDG uptake in a large area of the mid to distal anterior, anteroseptal, apical, and inferoapical walls. Polar map images (*top row*) demonstrated a large area of metabolic defect out of proportion to perfusion. **B**, Repeat PET images 3 months later showing marked improvement of myocardial F-18 FDG uptake in the anteroapical and inferoapical walls.

ported. Kurisu et al[18] assessed myocardial fatty acid metabolism in 14 patients with takotsubo cardiomyopathy using BMIPP and found that myocardial fatty acid metabolism is more severely impaired than myocardial perfusion. Taken together, the findings of the studies by Owa et al[17] and Kurisu et al and the findings in this report suggest that, in takotsubo cardiomyopathy, metabolism is uniformly reduced out of proportion to perfusion.

In conclusion, we report a case of takotsubo cardiomyopathy in which markedly reduced FDG uptake relative to perfusion was observed acutely, which resolved at follow-up, suggesting that myocardium stunning is the underlying condition of this syndrome.

Acknowledgment

The authors have indicated they have no financial conflicts of interest.

References

1. Tsuchihashi K, Ueshima K, Uchida T, Oh-mura N, Kimura K, Owa M, et al. Transient left ventricular apical ballooning without coronary artery stenosis: a novel heart syndrome mimicking acute myocardial infarction. J Am Coll Cardiol 2001;38:11-8.
2. Desmet WJ, Adriaenssens BF, Dens JA. Apical ballooning of the left ventricle: first series in white patients. Heart 2003;89:1027-31.
3. Bybee KA, Prasad A, Barsness GW, Lerman A, Jaffe AS, Murphy JG, et al. Clinical characteristics and thrombolysis in myocardial infarction frame counts in women with transient left ventricular apical ballooning syndrome. Am J Cardiol 2004;94:343-6.
4. Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, et al. Acute and reversible cardiomyopathy provoked by stress in women from the United States. Circulation 2005;111:472-9.
5. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G. Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 2005;352:539-48.
6. Abe Y, Kondo M. Apical ballooning of the left ventricle: a distinct entity? Heart 2003;89:974-6.
7. Braunwald E, Kloner RA. The stunned myocardium: prolonged, postischemic ventricular dysfunction. Circulation 1982;66:1146-9.
8. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 1. Circulation 2001;104:2981-9.
9. Dorbala S, Di Carli MF. Metabolic imaging of myocardial stunning. Heart Metab 2003;19:18-22.
10. Knabb RM, Bergmann SR, Fox KA, Sobel BE. The temporal pattern of recovery of myocardial perfusion and metabolism delineated by positron emission tomography after coronary thrombolysis. J Nucl Med 1987;28:1563-70.
11. Myears DW, Sobel BE, Bergmann SR. Substrate use in ischemic and reperfused canine myocardium: quantitative considerations. Am J Physiol 1987;25:H107-14.
12. Di Carli MF, Prcevski P, Singh TP, Janisse J, Ager J, Muzik O, et al. Myocardial blood flow, function, and metabolism in repetitive stunning. J Nucl Med 2000:41:1227-34.
13. Perrone-Filardi P, Bacharach SL, Dilsizian V, Marin-Neto JA, Maurea S, Arrighi JA, et al. Clinical significance of reduced regional myocardial glucose uptake in regions with normal blood flow in patients with chronic coronary artery disease. J Am Coll Cardiol 1994;23:608-16.
14. Liedtke AJ, Renstrom B, Hacker TA, Nellis SH. Effects of moderate repetitive ischemia on myocardial substrate utilization. Am J Physiol 1995;269:H246-53.
15. Kobayashi K, Neely JR. Effects of ischemia and reperfusion on pyruvate dehydrogenase activity in isolated rat hearts. J Mol Cell Cardiol 1983;15:359-67.
16. Shepherd PR, Kahn BB. Glucose transporters and insulin action—implications for insulin resistance and diabetes mellitus. N Engl J Med 1999;341:248-57.
17. Owa M, Aizawa K, Urasawa N, Ichinose H, Yamamoto K, Karasawa K, et al. Emotional stress-induced 'ampulla cardiomyopathy': discrepancy between the metabolic and sympathetic innervation imaging performed during the recovery course. Jpn Circ J 2001;65:349-52.
18. Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nishioka K, et al. Myocardial perfusion and fatty acid metabolism in patients with tako-tsubo-like left ventricular dysfunction. J Am Coll Cardiol 2003;41:743-8.