JACC Vol. 31, No. 6
May 1998:1440–8

LETTERS TO THE EDITOR

Paradoxical Sinus Deceleration During Dobutamine Stress Echocardiography

In the April 1997 issue of the Journal, Attenhofer et al. (1) observed paradoxical sinus deceleration in 14 (8%) of 181 patients during dobutamine stress echocardiography. Significant coronary artery disease was present in eight patients and absent in the remaining six. Activation of the Bezold-Jarish reflex, promoting reflex bradycardia, vasodilation and hypotension, is suggested as a probable mechanism.

In our experience, hypotension (systolic blood pressure decrease >30 mm Hg) without simultaneous deceleration of heart rate occurred in 8% of patients during dobutamine stress echocardiography (2). However, of 114 patients who also underwent coronary angiography for assessment of coronary artery lesions, heart rate increased in 12 of the 15 patients given a bolus of 1 mg of atropine, but only 2 patients achieved 85% of the maximal heart rate, and heart rate remained almost unchanged in 3 (2 without beta-adrenergic drugs). These three patients had significant coronary artery lesions (percent diameter stenosis >70%). Given the difficulty in achieving 85% of the maximal heart rate even in patients given atropine, heart rate changes as an indirect sign of atherosclerotic coronary artery disease were evaluated. We found that a heart rate <112 beats/min at the end of dobutamine stress echocardiography without treatment with beta-blockers showed a sensitivity of 65%, a specificity of 83% and a diagnostic accuracy of 73% for the diagnosis of coronary artery disease. In addition, heart rate <94 beats/min independently of the treatment received and abnormalities of myocardial contractility (multivariate analysis) showed a sensitivity of 69% and a specificity of 70% for the diagnosis of multivessel coronary artery disease (3).

In the study of Attenhofer et al. (1), although the number of patients treated with beta-blockers is not mentioned, seven of eight patients with significant coronary artery disease showed a heart rate <112 beats/min, and three of five patients with two- or three-vessel coronary disease showed a heart rate <94 beats/min. In the six patients without significant coronary artery disease, dobutamine stress echocardiography revealed myocardial contractility abnormalities in two, with atherosclerotic coronary lesions of percent diameter stenosis <50%. However, it is possible that a more accurate measurement of atherosclerotic lesions with the use of calipers could have resulted in a decrease in the number of false positive results.

Heart rate response to dobutamine stress echocardiography may include three possibilities: 1) acceleration up to 85% of maximal heart rate; 2) initial acceleration, followed by deceleration and hypotension through a vagal mechanism; and 3) limited increase in heart rate in patients with or without treatment with beta-blockers. In experimental studies, Vatner et al. (4) showed that in the absence of coronary artery disease, dobutamine increases heart rate in ~20% and cardiac contractility in 125%, whereas in the presence of coronary artery occlusion, there was an increase in heart rate and contractility of 15% and 32%, respectively, as opposed to exercise, in which case, heart rate increased by 102% and contractility decreased by 63%. Dobutamine directly stimulates adenosine triphosphate (ATP)- and cyclic adenosine monophosphate (cAMP)-dependent beta-adrenergic receptors, resulting in an increase in cardiac contractility and chronotropism. Stimulation of cAMP-independent alpha-adrenergic receptors causes an increase in cardiac contractility. In the initial phase of ischemia, there is a decrease in ATP production, which may induce a lower response to stimulation of beta-adrenergic receptors and, consequently, a lower chronotropic response (5,6) without alteration of cardiac contractility because these events occur when there is an important increase in heart rate (7).

MERCÈ CLADELLAS, MD
JORDI BRUGUERA, MD
LOUIS RECASENS, MD
JAUME ILLA, MD
Department of Cardiology
Hospital del Mar
Autonomous University of Barcelona
Passeig Maritim 25-29
E-08003 Barcelona, Spain

References

1. Attenhofer CH, Pellikka PA, McCully RB, Roger VL, Seward JB. Paradoxical sinus deceleration during dobutamine stress echocardiography: description and angiographic correlation. J Am Coll Cardiol 1997;29:994–9.
2. Cladellas Capdevila M, Bruguera Cortada J, Hernández Herrero J, Villena Segura J, Serrat Serradell R, Sardá R. Efectos secundarios de la ecografia de estrés con dobutamina. Rev Esp Cardiol 1996;49:22–8.
3. Cladellas M, Bruguera J, Grau J, Hernández J, Illa J, Sardá R. Signos predictores de enfermedad coronaria multivaso en la ecocardiografia con dobutamina. Rev Esp Cardiol 1997;50:772–7.
4. Vatner SF, McRitchie RJ, Maroko PR, Patrik TA, Braunwald E. Effects of catecholamines, exercise and nitroglycerin on the normal and ischemic myocardium in conscious dogs. J Clin Invest 1974;54:563–75.
5. Broadley KJ. Review of cardiac adrenoreceptors. J Auton Pharmacol 1982;2:119–45.
6. Tuttle RR, Millis J. Development of a new catecholamine to selectively increase cardiac contractility. Circ Res 1975;36:185–96.
7. Rude RE, Izquierdo C, Buja LM, Willerson JT. Effects of inotropic and chronotropic stimuli on acute myocardial ischemic injury. Circulation 1982;65:1321–8.

Reply

Cladellas et al. report their interesting observation that a maximal heart rate <112 beats/min with dobutamine stress echocardiography in the absence of beta-blocker medications indicates significant coronary artery disease with a diagnostic accuracy of 73%. Cladellas et al. believe that the insufficient heart rate increase during high dose dobutamine infusion results from a decrease in adenosine triphosphate production due to myocardial ischemia. However, in 17% of their patients, an insufficient heart increase to <112 beats/min was seen in the absence of coronary artery disease. Thus, in their experience, an attenuated chronotropic response cannot always be attributed to myocardial ischemia.

In the experimental study by Vatner et al. (1), the absolute heart rate increase with dobutamine was modest but similar with and without ischemia (16 and 15 beats/min, respectively), although the baseline heart rate was higher in dogs with ischemia. Thus, despite myocardial ischemia, the chronotropic response to dobutamine was intact. The duration of infusion of 40 μg/kg per min dobutamine was brief, 1 to 3 min, and differentiates that experimental work from the more prolonged infusion typically used with dobutamine stress echocardiography and probably accounts for the much smaller increment in heart rate than is usually observed during dobutamine stress echocardiography.

Our work (2) concerned the paradoxical heart rate decrease occasionally observed during dobutamine stress echocardiography. Thus, in all patients a higher heart rate was obtained during dobut-

0735-1097/98/$19.00
PII S0735-1097(98)00117-X

amine infusion before the decrease. By contrast, the observations of Cladellas et al. concern patients who failed to achieve an adequate heart rate response; it is not clear whether heart rate decrease occurred in any patient. As we reported, only 1 of 14 patients with paradoxical sinus deceleration was taking beta-blockers. We mentioned in our report that all our patients fasted for at least 3 h before dobutamine stress echocardiography; mild hypovolemia may have facilitated the occurrence of the vasodepressor response.

In our conclusions, we reported that paradoxical sinus deceleration was most often seen in patients with coronary artery disease, but in 14% of our patients with heart rate decrease, there were no angiographic, echocardiographic, electrocardiographic or clinical signs of coronary artery disease. Sinus deceleration was often accompanied by a decrease in blood pressure, nausea and chest pain. We believe that sinus deceleration during dobutamine stress echocardiography is typically mediated by the Bezold-Jarisch reflex and is most commonly seen in the presence of ischemia but may occur in its absence.

The echocardiographic signs of myocardial ischemia may be subtle if heart rate is not increased and can be best appreciated by continuous echocardiographic surveillance. Atropine is effective in increasing heart rate in patients with paradoxical bradycardia and is recommended in those with no manifestations of ischemia.

CHRISTINE H. ATTENHOFER JOST, MD
PATRICIA A. PELLIKKA, MD, FACC
Mayo Clinic
200 First Street SW
Rochester, Minnesota 55905

References

1. Vatner SF, McRitchie RJ, Maroko PR, Patrick TA, Braunwald E. Effects of catecholamines, exercise, and nitroglycerin on the normal and ischemic myocardium in conscious dogs. J Clin Invest 1974;54:563–75.
2. Attenhofer CH, Pellikka PA, McCully RB, Roger VL, Seward JB. Paradoxical sinus deceleration during dobutamine stress echocardiography: description and angiographic correlation. J Am Coll Cardiol 1997;29:994–9.

F-18 FDG Uptake in Transplanted Heart

In their recent report, Rechavia et al. (1) concluded that a threefold increase in the uptake of the glucose tracer analogue fluorine-18 2-deoxy-2-fluoroglucose (F-18 FDG) in transplanted hearts reflects a preference for glucose as a substrate. The authors further concluded that this preference for glucose may be due either to inefficient utilization of glucose by the transplanted heart or to the influence of circulating catecholamines.

This observation can be explained entirely by a change in the relation between F-18 FDG and glucose. The latter is commonly referred to as the "lumped constant" (LC) (2). This ratio between tracer (F-18 FDG) and tracee (glucose) reflects the kinetic differences between glucose and deoxyglucose transport and phosphorylation. Most studies have used a fixed value of 0.67 to quantitate glucose uptake from the F-18 FDG tracings (3–5), but we (6,7) and others (8) have recently observed in the isolated working heart that the LC is subject to significant variability, depending on the metabolic environment. Insulin and competing substrates to glucose cause a decrease in the LC (6–8), whereas epinephrine and ischemia can cause an increase in the LC (unpublished observations). An increase in the LC causes an overestimation of glucose uptake, whereas a decrease in the LC results in an underestimation of glucose uptake.

Thus, considering the results of Rechavia et al. (1) in light of the experimental findings (6–8), the concept of an increased LC in the transplanted hearts is in order. Such an increase would lead to the overestimation of glucose uptake. This effect may artificially introduce and accentuate otherwise minor differences in glucose uptake. The possibility of increased catecholamine sensitivity and the possible presence of chronic "demand ischemia" in transplanted hearts would argue in favor of this hypothesis.

A practical solution to this problem would be to determine the LC individually for every study from the time-activity curves of F-18 FDG accumulation (9). The results presented by Rechavia et al. (1) are undoubtedly interesting, but we caution against drawing any conclusions regarding the quantitation of glucose uptake or metabolism in transplanted human heart.

HEINRICH TAEGTMEYER, MD, DPHIL, FACC
TORSTEN DOENST, MD
Department of Internal Medicine
Division of Cardiology
University of Texas-Houston Medical School
6431 Fannin, MSB 1.246
Houston, Texas 77030
E-mail: ht@heart.med.uth.tmc.edu

References

1. Rechavia E, De Silva R, Kushwaha SS, et al. Enhanced myocardial 18F-2-fluoro-2-deoxyglucose uptake after orthotopic heart transplantation assessed by positron emission tomography. J Am Coll Cardiol 1997;30:533–8.
2. Sokoloff L, Reivich M, Kennedy C, et al. The [^{14}C] deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. J Neurochem 1977;28:897–916.
3. Gambhir SS, Schwaiger M, Huang SC, et al. Simple noninvasive quantification method for measuring myocardial glucose utilization in humans employing positron emission tomography and fluorine-18 deoxyglucose. J Nucl Med 1989;30:359–66.
4. Knuuti MJ, Nuutila P, Ruotsolainen U, et al. The value of quantitative analysis of glucose utilization in detection of myocardial viability by PET. J Nucl Med 1993;34:2068–75.
5. Stone CK, Holden JE, Stanley W, Perlman SB. Effect of nicotinic acid on exogenous myocardial glucose utilization. J Nucl Med 1995;36:996–1002.
6. Hariharan R, Bray MS, Ganim R, Doenst T, Goodwin GW, Taegtmeyer H. Fundamental limitations of [^{18}F] 2-deoxy-2-fluoro-D-glucose for assessing myocardial glucose uptake. Circulation 1995;91:2435–44.
7. Russell RR, Mrus JM, Mommesin JI, Taegtmeyer H. Compartmentation of hexokinase in rat heart: a critical factor for tracer kinetic analysis of myocardial glucose metabolism. J Clin Invest 1992;90:1972–7.
8. Ng CK, Holden JE, DeGrado TR, Raffel DM, Kornguth ML, Gatley SJ. Sensitivity of myocardial fluorodeoxyglucose lumped constant to glucose and insulin. Am J Physiol 1991;260:H593–603.
9. Kuwabara H, Evans A, Gjedde A. Michaelis-Menten constraints improved cerebral glucose metabolism and regional lumped constant measurements with [^{18}F]fluorodeoxyglucose. J Cereb Blood Flow Metab 1990;10:180–9.

Reply

In their comment on the report by Rechavia et al. (1), Doenst and Taegtmeyer make several important statements about the lumped constant (LC) for fluorine-18 2-fluoro-2-deoxy-D-glucose (F-18 FDG) and how changes in this variable would reflect on the quantitative assessment of myocardial glucose utilization with this method. They also surmize how the LC may differ between fasting conditions in normal subjects and in transplant recipients.

We agree with the view that it is important to develop an understanding of how the kinetics of F-18 FDG and glucose differ under varying pathophysiologic conditions in humans, but the absence of appropriate and unequivocal data means that predictions of how the LC might change clinically are still clearly speculative.