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Reply

In response to Boudoulas and Leier, our findings with zatebradine do not just relate to a lack of an additive effect on exercise tolerance when the drug is administered to patients with angina pectoris already receiving nifedipine (1). There are reports showing that zatebradine is less effective than long-acting diltiazem on exercise tolerance when used as monotherapy (2) in patients with angina pectoris and no different from placebo in double-blind randomized trials (3). There are also data suggesting that zatebradine is less effective than propranolol in patients with angina pectoris despite similar reductions in heart rate. It is the combination of these clinical experiences that made us propose that negative inotropy or some metabolic protective action, or both, may be more important than heart rate reduction in the antianginal effects of rate-lowering calcium-entry and beta-adrenergic blocking agents (4). This is also suggested by the successful experience of Moss et al. (5) in using internal pacing to increase heart rate when using high dose beta-blockade to relieve symptoms in patients with refractory angina pectoris and bradycardia.

We did not evaluate diastolic time, systolic ejection time, collateral function or indexes of left ventricular function in our study and cannot respond to some of the specific remarks raised by Boudoulas and Leier.

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Dobutamine Stress Echocardiography in Orthotopic Heart Transplant Recipients

We read with great interest the report by Derumeaux et al. (1) on the evaluation of transplant coronary artery disease by dobutamine stress echocardiography. The authors deserve to be commended for using quantitative coronary angiography as the reference standard to compare the dobutamine stress echocardiographic findings. However, we would like to comment on the methods utilized to calculate sensitivity, specificity and positive and negative predictive values, which may have important implications on their findings. In their study (1), the authors used quantitative coronary angiography as the reference standard to evaluate the diagnostic accuracy of dobutamine stress echocardiography in 37 patients. They report a sensitivity and specificity of 86% and 91%, respectively. The problem is that these values (sensitivity, specificity, positive and negative predictive values) are not based on the comparative analysis of the results of dobutamine stress echocardiography versus those of quantitative coronary angiography. To derive the values the authors made two major assumptions: 1) Any inducible wall motion abnormality observed was attributable to the mere presence of focal epicardial coronary angiographic lesions rather than significant (>50%) lesions. 2) All focal epicardial coronary lesions were considered physiologically significant regardless of degree of stenosis. For example, in their study, seven patients with mild angiographic lesions (<40%) were considered to have true positive results solely on the basis of the positive results by dobutamine stress echocardiography. Obviously, this creates major problems in the analysis of sensitivity, specificity and positive and negative predictive accuracy. It is inconsistent to first use a test (quantitative coronary angiography in this case) as a reference standard to assess the accuracy of dobutamine stress test results and then later to incorporate insignificant coronary lesions as angiographically abnormal. For instance, when stress echocardiography results were positive in the presence of angiographic lesions as minimal as 15% stenosis, they were considered "true positive" in the calculation of sensitivity, specificity and positive and negative predictive values.

Without adhering to strict criteria based on quantitative angiography (reference standard), it may be difficult to know the false positive rate of dobutamine stress echocardiography in heart transplant recipients. Most investigators consider ≥50% stenosis angiographically significant stenosis (2–5). The authors correctly point out the limitations of coronary angiography in assessing lesion severity in heart transplant recipients. Coronary angiography is known to underestimate the severity of underlying coronary artery disease in heart transplant recipients (6). However, at present, it is premature to consider dobutamine stress echocardiography the diagnostic test of choice for transplant coronary artery disease and as a substitute for coronary angiography as the reference standard.

Using standard criteria for defining significant coronary disease by nonquantitative coronary angiography, we derived the sensitivity and specificity in 41 transplant recipients (2). The sensitivity and specificity were 95% and 55%, respectively, and the negative and positive predictive values were 92% and 76%, respectively (2). In the current