

### References

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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  $\geq 50\%$  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

study by Derumeaux et al. (1) it is not possible to calculate specificity because we do not know the actual false positive rate. For instance, does an abnormal response on the dobutamine stress test in a patient with 15% coronary stenosis represent a false positive result on the dobutamine stress echocardiogram or a false negative result on the coronary angiogram? If one recalculates their data taking into account angiographic stenosis  $\geq 50\%$  as the reference for significant disease, different values for sensitivity, specificity and positive and negative predictive values emerge. The sensitivity, specificity and positive and negative predictive values are 100%, 77%, 50% and 100%, respectively. Thus, the recalculated estimate of high sensitivity and negative predictive value can be interpreted to suggest that dobutamine stress echocardiography is an excellent screening test for transplant coronary artery disease and is consistent with our previous report (2). Finally, it can be hypothesized that compared with angiography, dobutamine stress echocardiography is more sensitive for the small-vessel coronary disease frequently observed in heart transplant recipients but severely underestimated by coronary angiography. However, the extent to which this hypothesis is true can only be determined by large multicenter clinical studies. Evaluation in experimental models of transplant atherosclerosis may also be necessary to allow direct morphologic and histopathologic correlation of observed underestimation of angiographic findings in transplant coronary artery disease in humans.

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#### Reply

Akosah and Mohanty express their concern about the method we used to establish the sensitivity and specificity of dobutamine stress echocardiography in 37 heart transplant recipients (1). They thought it inconsistent that we incorporated insignificant coronary lesions as angiographically abnormal. We remind them that we clearly defined three groups of patients according to the results of quantitative coronary angiography, as follows: *group 1* = normal results on coronary angiography; *group 2* = nonsignificant coronary lesions ( $<50\%$  stenosis); *group 3* = significant coronary lesions ( $>50\%$  stenosis). We clearly gave the results of dobutamine stress echocardiography in each group of patients: *group 1* = 2 of 23 positive test results; *group 2* = 5 of 7 positive test results (i.e., sensitivity 71%); *group 3* = 7 of 7 positive test results (i.e., sensitivity 100%). Therefore, the overall sensitivity of dobutamine stress echocardiography was 86%, whereas that for specificity was 91%.

Dobutamine stress echocardiography is designed to detect ischemia, whereas coronary angiography detects stenosis. In a recent study, Baptista et al. (2) established from receiver-operating curves the angiographic cutoff values with the best predictive value for the development of ventricular wall motion abnormalities during dobutamine stress echocardiography in 34 patients with conventional atherosclerotic coronary lesions. They found a 52% diameter stenosis to have functional significance, with occurrence of wall motion abnormalities during dobutamine stress echocardiography. However, it is now well established that graft atherosclerosis differs from conventional atherosclerosis because of extensive, diffuse, concentric lesions related to a fibrous intimal hyperplasia that may be associated with focal stenosis (3). Therefore, coronary angiography may consistently underestimate epicardial coronary stenosis, as recently assessed by intracoronary ultrasound (4), and percent stenosis is a poor predictor of the functional significance of these diffuse coronary lesions. That is the reason why we evaluated the sensitivity of dobutamine stress echocardiography to detect ischemia in heart transplant recipients with mild lesions, usually considered nonsignificant by quantitative coronary angiography. Moreover, we recently demonstrated (5) that the positivity of dobutamine stress echocardiography in patients with mild lesions may be related to smaller diameters of apparently healthy coronary segments.

Therefore, we conclude that dobutamine stress echocardiography is the noninvasive test of choice to detect ischemia related to graft atherosclerosis, even when coronary artery lesions appear to be nonsignificant on coronary angiography.

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### Preinfarction Angina as a Major Predictor of Left Ventricular Function and Long-Term Prognosis After a First Q Wave Myocardial Infarction

Anzai et al. (1) report that preinfarction angina is associated with a favorable in-hospital course and improved survival in patients with a first Q wave myocardial infarction. The presence of preinfarction