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 ≥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

angina had a favorable effect on the incidence of ventricular arrhythmias and late-phase ventricular function. Because their patients with and without preinfarction angina were similar in treatment delay from onset of symptoms, revascularization therapies, angiographic success rate, collateral supply to the infarct region, severity and extent of coronary artery disease, they propose that ischemic preconditioning may be responsible for this protection.

Anzai et al. rightly point out that mechanisms other than acute collateralization could be responsible for protection seen in patients with preinfarction angina. They do not provide coronary recanalization times in the two groups. However, the duration of coronary occlusion is a major determinant of the extent of myocardial necrosis and infarct size. We previously showed (2) that 49% of patients presenting with myocardial infarction show spontaneous intermittent recanalization of the infarct-related coronary artery before administration of thrombolytic treatment (*intermittency*) and that this intermittency is associated with greater hemostatic activity. Furthermore, a large proportion of patients with intermittency have preinfarction angina. Intermittency and preinfarction angina appear to represent a slower mode of evolution of the process of coronary thrombosis and acute myocardial infarction (2). It is conceivable that the infarct-related arteries of such patients are more amenable to recanalization because fresh thrombi are lysed comparatively easily, both by intrinsic fibrinolysis, leading to intermittency, and by therapeutic measures, resulting in faster coronary recanalization. Thus, reperfusion associated with intermittency may protect myocardium by providing intermittent nutrient flow to the area at risk, by facilitating faster recanalization after thrombolytic therapy (3) or by preconditioning the myocardium.

Interestingly, intermittency can have a dual effect on the incidence of ventricular arrhythmia during acute myocardial infarction. We recently showed that intermittency is associated with a higher incidence of ventricular arrhythmia in the first 6 h of infarction but a lower incidence between 18 and 24 h (4). This delayed protection is independent of treatment delay, coronary recanalization time and 90-min patency of the infarct-related coronary artery and is consistent with the "second window of protection" seen in the experimental studies (5).

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Reply

Haider and Davies state that an unexpectedly large proportion of patients with acute myocardial infarction showed intermittent recanalization, as evidenced by transient regression of ST segment elevation on ambulatory electrocardiographic (ECG) monitoring, and that this phenomenon was related to protection of myocardial damage (1). There were diverse effects of spontaneous ST segment regression on ventricular arrhythmia (i.e., higher incidence of ventricular arrhythmia in the early phase but a lower incidence in the late phase) (2). They suggested that intermittent reperfusion had a protective role against myocardial damage through the preconditioning effect because there was no significant difference in recanalization time between the groups with and without intermittent ST segment regression, although it tended to be shorter in patients with than without ST regression. Recently, they also examined the effect of the presence of preinfarction angina on recanalization time in patients with acute myocardial infarction who received thrombolytic therapy and found that the recanalization time was earlier in patients with than without preinfarction angina, although the study cohort was limited (3).

We do not have any data on continuous monitoring of the ST segment, and therefore we cannot discuss this explanation with certainty. We also cannot exclude such a possibility in our study cohort. Our study was concerned with the effects of preinfarction angina on infarct expansion and ventricular remodeling and included patients with a first anterior or inferior Q wave infarction who did not undergo reperfusion therapy, as well as those who did (4). In contrast, their study cohort included patients who underwent thrombolytic therapy. Furthermore, their cohort included patients with a prior infarction, which potentially affected the results.

In our study, coronary revascularization therapy was attempted in patients <75 years old who arrived within 6 h after the onset of acute myocardial infarction. The percentage of patients who arrived within 6 h after the onset was similar in those with and without preinfarction angina, as we have shown (4,5). There was also no difference in the time that reperfusion therapy was initiated between the two groups. The angiographic success rate was not different between patients with and without preinfarction angina. Patients who underwent reperfusion therapy encompassed only 39% of the cohort, and angiographically documented reperfusion was confirmed in only some of the patients. Another 61% who did not undergo reperfusion therapy also showed a better clinical outcome in the presence of preinfarction angina (4). This finding suggests that some additional mechanisms played a role in the favorable clinical outcome. Although intermittent reperfusion may have played a protective role in patients with preinfarction angina, we have no clear evidence to support this phenomenon, at least in the study cited by Haider and Davies.

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