dipyridamole stress echocardiography versus perfusion scintigraphy. In contrast to Fragasso et al., Astarita et al. used a "state-of-the-art" atropine protocol, and they in fact observed that dipyridamole sensitivity was raised to 88%. Stress echocardiography protocols have evolved rapidly in recent years. When the diagnosis is the target, atropine coadministration should be used. When prognostic stratification is the reason for testing, a high dose without atropine, even in hypertensive patients (6), provides excellent stratification (7).

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REPLY

We are grateful to Dr. Varga for his comments on our report (1), because his letter gives us the opportunity to further clarify our opinion. Like others (2), in the past, we have used dipyridamole for the diagnosis of coronary artery disease, but we (3) have been unable to reproduce the diagnostic accuracy reported by some groups. Interestingly enough, the near totality of these data comes from a single institution. In our study, we decided not to use atropine to assess the intrinsic strength of the individual stressors. The sensitivities and specificities for perfusion scintigraphy, dipyridamole and dobutamine echocardiography were 98% and 36%, 61% and 91%, 88% and 80% respectively. As a consequence, accuracy, which takes in account both sensitivity and specificity, was not significantly different between the three tests, although dobutamine appeared to perform better (84%) than dipyridamole (74%) and scintigraphy (71%). Furthermore, in patients with one-vessel disease, the performance of dipyridamole was very poor, with a sensitivity of 31%. We do not think that the addition of atropine could have increased this figure to an acceptable level, especially if we take into account that, in this subgroup, the sensitivities of dobutamine and scintigraphy were 85% and 95%, respectively. Indeed, we believe that such differences are enough to justify our statement that dobutamine echocardiography (as well as rest/stress myocardial perfusion scintigraphy) are better than dipyridamole echocardiography in these patients. We cannot afford the risk of missing so many patients with coronary artery disease in such a high-risk group. In addition, this statement is also justified by pathophysiologic considerations. Dobutamine increases oxygen demand by increasing contractility, heart rate and systolic blood pressure. These features make dobutamine an ideal stressor in hypertension. In contrast, dipyridamole produces coronary vasodilation, with little "myocardial stress," as defined by changes in the rate–pressure product and a lesser likelihood of causing myocardial ischemia. This is why dipyridamole yields high sensitivities when used with scintigraphy, where perfusion abnormalities are thought to represent areas of altered blood flow rather than areas of ischemia; however, this is also why its sensitivity is low when used with echocardiography.

Surely, the addition of atropine improves sensitivity, but it also leaves misdiagnosed a large proportion of patients with single-vessel disease. Furthermore, although dipyridamole is considered a safe test, most patients experience considerable side effects. Aminophylline is administered at the end of the test, and, when atropine has also been given, sustained sinus tachycardia usually ensues, causing discomfort and making the duration of the test as long as dobutamine testing. On the basis of these considerations, we think that dobutamine provides the best performance for the diagnosis of coronary artery disease in hypertensive patients (and beyond). Our feeling (allowed in a letter!) is that most cardiologists around the world share the same opinion.

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Overdosing With Prostacyclin in Primary Pulmonary Hypertension

Rich and McLaughlin (1) reported excessively high rest cardiac outputs in 12 of 55 patients with primary pulmonary hypertension (PPH) treated with intravenous prostacyclin, all of whom had

follow-up right heart catheterization. As they point out, the intravenous dosing of prostacyclin, which has been so helpful in increasing exercise tolerance and prolonging life in patients with PPH, is complex. The practice has been to maximize dose at the time of initiation of treatment and then to adjust the dose according to symptomatology. The average rest cardiac index was 7.4 liters/min per m^2 in these patients. They proceeded to reduce the dose of prostacyclin, on the basis of repeat cardiac output and hemodynamic measurements, until they reduced the rest cardiac index to 4.0 liters/min per m^2. This resulted in an average dose reduction of 39%, with virtually no change in pulmonary artery pressure. They did not report any data on the effect of the dose reduction on the patients' exercise performance (e.g., peak oxygen consumption [$\dot{V}O_2$] or anaerobic threshold), which is obviously the important question because exercise limitation is the major symptom in these patients.

From the Fick principle for measuring cardiac output, it is obvious that $\dot{V}O_2$ is a proxy variable of cardiac output. The dose of the drug that provides the highest peak $\dot{V}O_2$ during exercise is therefore also the dose that provides the maximally effective cardiac output response to exercise (2). The maximal cardiac output that provides effective perfusion to the tissues without developing lactic acidosis, and therefore is the sustainable level of exercise, is the anaerobic threshold, a measurement obtained by measuring carbon dioxide consumption ($\dot{V}CO_2$) concurrently with $\dot{V}O_2$. The oxygen pulse ($\dot{V}O_2$/heart rate), measured during the same test, is equal to the stroke volume × arteriovenous oxygen difference, and correlates well with stroke volume as measured by the direct Fick method. The slope of expired volume ($\dot{V}E$) versus $\dot{V}CO_2$ is consistently high in patients with PPH, because it reflects hypoperfusion to the ventilated lung. Thus, as recently reported by Wax et al. (3), cardiopulmonary exercise testing provides a valuable noninvasive marker that can be useful in guiding therapy.

Cardiopulmonary exercise testing provides a comprehensive, quantitative, noninvasive assessment of cardiovascular and respiratory function. In preliminary studies of sequential cardiopulmonary exercise testing in patients with PPH treated with prostacyclin, we found that a maximal benefit is achieved despite increasing dosage. The failure to improve variables of aerobic function and ventilatory efficiency in response to exercise logically sets the optimal dose.

The high rest cardiac output values reported by Rich and McLaughlin are counter to those expected in patients with PPH, and therefore the mechanism would be interesting to address. They attributed the high rest cardiac outputs to increased inotropy caused by prostacyclin. They did not provide stroke volume measurements to support this suggestion. The very flushed skin of these patients suggests another explanation. Perhaps the reduced systemic resistance decreased left ventricular afterload. This may decrease pressure in the left atrium below that of the right atrium, thereby diverting right atrial blood through a foramen ovale. The blood flow through the foramen ovale is a right to left shunt, but the high skin blood flow is functionally a left-to-right shunt.

Prostacyclin is not a selective pulmonary vasodilator. It dilates the systemic circulation as well as the pulmonary circulation. Because of the pulmonary arteriopathy in PPH, dilation of the pulmonary circulation is likely to be more limited than that of the systemic circulation. Thus, if pulmonary vascular disease limits the ability to further recruit and dilate pulmonary blood vessels beyond a certain point with an increasing dose, further dosing will just dilate the systemic circulation with no benefit to the patient. In fact, the unneeded vasodilation may be detrimental to the patient, as Rich and McLaughlin suggest.

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