Editorial Comment

Myocardial Ischemia During Pharmacological Stress Testing

Abdulmassih S. Iskandrian, MD

Myocardial perfusion imaging and two-dimensional echocardiography during dipyridamole- or adenosine-induced coronary hyperemia have been used increasingly in the diagnosis of coronary artery disease (CAD) and in risk assessment.1-5 The mechanism of action of adenosine involves activation of cell surface, purine A1 and A2 receptors. The mechanism of action of dipyridamole is indirect via inhibition of cellular reuptake of endogenous adenosine.1,3,6 In both types of stress imaging, adenosine induces increases in coronary blood flow. The reduction in regional coronary vasodilator reserve in the presence of coronary stenosis provides a simple model that explains the relative perfusion deficits in most CAD patients.1,3,7 A more complex model is required to explain the presence of myocardial ischemia during adenosine vasodilation, which, unlike exercise, cannot be explained by an increase in myocardial oxygen demand. Adenosine is “antiadrenergic” through decreasing adenyl cyclase and cyclic AMP. A widely accepted explanation for adenosine-induced ischemia is the presence of coronary steal, either “vertical” (intercoronary or collateral dependent) or “horizontal” (epicardial steal from the endocardium).

See p 1211

In the collateral-dependent steal model, the collaterals are intercoronary rather than intracoronary, and the steal occurs by reducing collateral flow into a severely stenosed receiving artery via excess flow into the perfusion bed of the collateral supply artery. The degree of steal depends on the supply artery resistance, receiving artery resistance, and collateral conductance.8-12 The contribution of collateral flow to the overall flow in the receiving artery at baseline directly affects the degree of steal during coronary vasodilatation; a larger contribution begets a greater steal. In the classic example of intercoronary steal, a mild stenosis in the collateral supply artery proximal to the origin of collaterals is present, although the normal anatomical tapering may provide sufficient inherent resistance to create a mild pressure gradient. The degree of steal probably is more in the presence than absence of stenosis in the collateral supply artery.11 Coronary steal depends on distal pressure in the supply artery; in dogs with well-developed collaterals, maintaining the blood pressure by α-agonists during dipyridamole infusion can prevent coronary steal. Conceivably, use of calcium channel blockers and nitrates to dilate epicardial arteries and stenosis segments also may decrease the pressure drop and maintain collateral flow.12,13

What are the markers of myocardial ischemia during pharmacological testing? Documentation of ischemia is not always easy in humans because of limitations of techniques for measuring absolute coronary blood flow, collateral flow, and transmural flow distribution. Positron emission tomography (PET) can measure absolute regional coronary blood flow but cannot distinguish epicardial from endocardial flow.14 Demer et al15 measured regional tracer activity of 13N ammonia or 82Rb and showed a decrease in activity during dipyridamole infusion (compared with rest) in collateralized vessels. Metabolic evidence of ischemia (increased regional concentration of 18F-fluorodeoxyglucose) was observed in some segments with perfusion defects during dipyridamole infusion.16

Demonstration of new or worsening of preexisting wall motion abnormality is good evidence of ischemia. However, the prevalence of this finding during adenosine vasodilation varies between 10% and 90%.3,4,7,17-19 In patients with multiple perfusion defects due to multivessel CAD, it is conceivable that some of the perfusion abnormalities may be due to steal and others due to disparity in vasodilator reserve. This may explain why perfusion defects are more common than wall motion abnormalities.

The possible reasons for the variability in the prevalence of wall motion abnormality have been discussed recently.19 Picano et al17 found that the increase in the great cardiac vein flow was less in patients with than in those without dipyridamole-induced wall motion abnormality (by two-dimensional echocardiography). However, they did not observe a net decrease in flow.17 ST depression has been reported in 10-70% of patients during pharmacological coronary vasodilatation.1,18,20 We and others1,20 have found no correlation between ST depression and extent of CAD or extent and severity of perfusion abnormality.

In this issue of Circulation, Nishimura et al21 report that angiographic presence of collaterals was the strongest predictor of ST depression (odds ratio, 23; 95% confidence interval, 4-144) during adenosine vasodila-
tion. In this study, 22 of the 65 patients (34%) with reversible thallium defects during adenosine infusion had ST depression, and 43 (66%) did not. Angiographically visible collaterals were seen in 18 patients (82%) with ST depression but in only 10 patients (23%) without ST depression (p<0.001). On multivariate stepwise logistic regression analysis, three variables were predictors of ST depression: collaterals, resting systolic blood pressure, and typical angina pectoris. The importance of collaterals suggests the possibility of myocardial ischemia due to steal. A similar relation between ST depression and collaterals has also been noted during dipyridamole infusion. Because of differences in plasma half-life and mechanism of action, ST depression tends to occur during adenosine infusion but after dipyridamole infusion. Although the study by Nishimura et al. showed a correlation between collaterals and ST depression, it did not prove that either coronary steal or ischemia actually occurred in these patients. However, in the study by Latanzi et al., 91% of 57 patients with CAD showed regional wall motion abnormality during dipyridamole infusion, and ST depression was noted in 70% of these patients. When these patients were treated with antianginal medications and restudied, wall motion abnormality and ST depression were less frequent (65% and 51%, respectively). These findings suggest a close relation between wall motion abnormality, a marker of ischemia, and ST depression during dipyridamole infusion.

Evidence of myocardial ischemia may also be inferred from hemodynamic evaluation. We measured the pulmonary capillary wedge pressure, cardiac output, and right heart pressures at baseline and during adenosine infusion and correlated these findings to simultaneously acquired thallium tomographic images. In normal subjects, there was a slight increase in pulmonary capillary wedge pressure during adenosine infusion, most likely due to increased myocardial turgor and stiffness associated with coronary hyperemia. In 30–40% of CAD patients, the increase in the pulmonary capillary wedge pressure was greater than that observed in normal subjects. These patients also had prominent V waves in the pulmonary capillary wedge pressure tracings. The increase in pulmonary capillary wedge pressure was greater in CAD patients with than in those without collaterals. These changes were observed despite preservation of regional and global systolic left ventricular function and in the absence of mitral regurgitation by contrast left ventriculography; they suggest the development of ischemia-induced diastolic left ventricular dysfunction in addition to the “physiological” response secondary to hyperemia.

Thallium variables of importance to the concept of ischemia include increased lung thallium uptake and left ventricular cavity dilatation. Qualitative (or quantitative) evidence of increased lung thallium uptake is strongly suggestive of ischemic left ventricular dysfunction. In the study by Nishimura et al., there was a trend toward more patients with than without ST depression (32% versus 14%) having increased lung thallium uptake, although the difference did not reach a statistically significant level. The increased lung thallium uptake may depend on the extent of ischemic dysfunction.

Finally, symptoms during adenosine or dipyridamole infusion should also be considered predictive of ischemia. Chest pains are frequent, but they tend to occur in patients both with and without CAD. They are most likely due to activation of A1 rather than A2 receptors. Adenosine may be the biochemical signal for cardiac ischemic pain, and thus it may not be possible to distinguish typical angina from pain induced by exogenous adenosine. The distinction between typical angina and nonspecific pains is not always easy, but if feasible, typical angina was a predictor of ST depression in the study by Nishimura et al (odds ratio, 10; 95% confidence interval, 1.7–57). Dyspnea is another common complaint (due to direct stimulation of chemoreceptors), but it also occurs in patients with and without CAD.

Finally, by suggesting a strong association between ST depression and collaterals, the report by Nishimura et al raises an important issue related to prognosis. Collateral flow has been shown in animal and clinical studies to reduce infarct size. Is it possible that ST depression, a marker of well-developed collaterals, identifies patients who are at lower (and not higher) risk? If so, this will be a striking difference from the experience with exercise testing. Bolognesi et al did not find a difference in the prognosis of post–myocardial infarction patients based on the presence or absence of angina during dipyridamole infusion. The event rate, however, was higher in patients with than without ST depression (personal communication). Thus, of 130 CAD patients without ST depression, 21 (16%) had one or more cardiac events (18 nonfatal reinfarctions, and one cardiac death), whereas among the 90 patients with ST depression, 31 (34%, p<0.01) had cardiac events (26 unstable angina, two reinfarctions, and three cardiac deaths).

The current study provides additional evidence that some patients (one of three) may have true myocardial ischemia induced during adenosine and that induction of ischemia is in part dependent on intervessel collaterals. This implies that in the majority of patients with adenosine-induced “steal,” ischemia is due to intercoronary steal rather than to epicardial-endocardial steal. Two thirds of the patients studied had perfusion defects without evidence of ischemia.

References


KEY WORDS • adenosine • dipyridamole • coronary artery disease • myocardial ischemia • pharmacology • stress • Editorial Comments
Myocardial ischemia during pharmacological stress testing.
A S Iskandrian

Circulation. 1993;87:1415-1417
doi: 10.1161/01.CIR.87.4.1415

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1993 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/87/4/1415.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at: http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at: http://circ.ahajournals.org/subscriptions/