The Adenosine Saga: One More Piece of the Puzzle
But Does It Cause Wall Motion Abnormalities?

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The novice who develops a genuine curiosity about adenosine will first marvel at the ubiquity of this small (molecular weight, 267) molecule, which participates in a wide variety of physiological processes in virtually every cell of the body. Second, the uninitiated may be appalled by the sheer volume of scientific information that has been amassed on the physiological and pharmacological properties of adenosine since Drury and Szent-Gyorgyi’s landmark report more than half a century ago clearly documented the potent coronary vasodilator effect of adenosine. Third, the novice may begin to ponder the remarkable paradox between such a wealth of scientific knowledge and the relatively scanty amount of clinical information on adenosine. For it was not until the past few years that clinicians at last became interested in this exciting compound.

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Sollevi et al2 were among the first to use adenosine with a therapeutic purpose, as a practical means to induce and maintain controlled systemic hypotension during intracranial vascular surgeries. In anesthetized patients who received an intravenous infusion of 100–320 µg·kg–1·min–1 of adenosine, these investigators demonstrated a 43% decrease in mean arterial pressure, a 17% increase in heart rate, a 61% decrease in systemic vascular resistance, a 44% increase in cardiac output, and a 37% decrease in cerebral arteriovenous oxygen difference. An increase of about 15% occurred in mean pulmonary arterial pressure and pulmonary arterial wedge pressure.

In the 1980s, several groups3–4 proposed the use of intravenous boluses of adenosine as a highly efficacious treatment for paroxysmal supraventricular tachycardia. When administered in this fashion, adenosine slows the AV conduction, thus interrupting the reentry pathway and terminating these arrhythmias. This is to date the only clinical application of adenosine that is approved by the US Food and Drug Administration, although it has been suggested that adenosine may also terminate exercise-induced ventricular tachycardia.5

In the past few years, several investigators have assessed intravenous infusion of adenosine in combination with myocardial perfusion scintigraphy as a means to demonstrate coronary artery disease.6–9 This was a natural development, because dipyridamole, which acts by increasing adenosine blood and tissue levels, has been used with the same purpose for more than a decade, although it was only recently approved for this use in the United States. In fact, ethyl adenosine and later adenosine were used to demonstrate perfusion abnormalities by 201Tl scintigraphy in dogs with experimental coronary stenosis10,11 several years before adenosine was first administered to human beings as a coronary vasodilatory stimulus.

A very desirable property of exogenously administered adenosine is its ultrashort half-life of only a few seconds, which accounts for the rapid resolution of its effects (and side effects) within 1 or 2 minutes of discontinuation of its administration. Despite its recent introduction, a large amount of experience has already been accumulated with adenosine perfusion imaging in several institutions in the United States.6–9 Most investigators thus far have used 201Tl as the coronary flow tracer, but adenosine perfusion imaging has also been found to work well with 99mTc teboroxime12 and with positron emission tomography.13 Under these circumstances, the use of short-lived coronary flow tracers (such as the positron emitters) or tracers with rapid myocardial washout (such as teboroxime) in combination with transient adenosine-induced coronary vasodilation enable acquisition of stress and rest images in <1 hour. Adenosine scintigraphy is also suitable with 99mTc sestamibi as the coronary flow tracer (M.S. Verani, unpublished observations).

A very appropriate concern, however, regarding the administration of adenosine to human beings is its safety, particularly in view of the possibility of inducing coronary steal and severe myocardial ischemia, both of which have been documented in laboratory animals. In addition, adenosine may also induce transient atrioventricular block in a small fraction of patients.6–9,14,15 Although an even larger amount of experience will clearly be welcome, several groups have documented the safety of an intravenous infusion of adenosine at doses of 140 µg·kg–1·min–1 for several minutes in patients with coronary artery disease.
In this issue of *Circulation*, Ogilby et al describe new changes in subjects provoked by adenosine in both normal subjects and patients with coronary artery disease. The most striking and interesting finding was an inordinate (and sometimes unexpected) elevation of the pulmonary arterial wedge pressure, which reached levels ordinarily thought to lead to pulmonary edema if they persist for some time. One would be tempted to attribute it to an increase in lung thalium uptake, which has been reported in some patients during adenosine scintigraphy, to the increase in pulmonary artery wedge pressure, but Ogilby et al did not find a correlation between these two variables. Although the authors did not obtain high-fidelity pressure/volume loops, which would have been enlightening, their findings of a marked elevation in pulmonary capillary wedge pressure in the presence of little change in ventricular volume nonetheless suggests a transient decrease in left ventricular distensibility.

One might speculate that this decrease in distensibility is secondary to acute myocardial ischemia, perhaps as a result of adenosine-induced coronary steal. Alternatively, the increased coronary flow velocity during adenosine infusion might produce collapse of severe stenoses because of decreased intraluminal distal perfusion pressure. As Ogilby and coworkers point out, several lines of evidence argue against both of these explanations. First, the elevated wedge pressures occur not only in patients with coronary artery disease but also, albeit to a lesser extent, in normal subjects. Second, electrocardiographic evidence of myocardial ischemia is the exception rather than the rule during adenosine infusion. Third, and most important, was the very low frequency of transient wall motion abnormalities and the absence of stenosis collapse during adenosine administration, which the investigators demonstrated by repeat contrast ventriculography and coronary angiography during adenosine infusion in selected patients. The low frequency of wall motion abnormalities must be tempered by the authors’ use of single-plane contrast angiography in the right anterior oblique view, which does not allow evaluation of the septum and the posterolateral wall of the left ventricle. Moreover, Ogilby and coworkers used a suboptimal method for assessing wall motion abnormalities.

Nonetheless, lacking support for an ischemic mechanism, the authors entertained other possible explanations for an adenosine-induced decrease in ventricular compliance. Most attractive is the hypothesis of a “hydraulic” effect or “myocardial erection,” which has been clearly demonstrated to occur in isolated, perfused rabbit hearts during high coronary flow states and is caused by engorgement of the ventricular walls with blood. In fact, in Vogel’s experimental preparation, very substantial elevations of the left ventricular diastolic pressures were documented, associated with a shift to the left of the ventricular pressure–volume curve. This shift was more pronounced at larger ventricular volumes and in the hearts subjected to prolonged myocardial ischemia. Although this “myocardial erectile” phenomenon is not uniformly accepted by all physiologists, it provides a logical framework to explain the hemodynamic changes observed by Ogilby and coworkers. A greater increase in pulmonary arterial wedge pressure in coronary patients than in normal subjects could be explained by either a large resting diastolic volume or an increased ventricular stiffness, both secondary to chronic myocardial ischemia or fibrosis. In some patients, perhaps those who also have concomitant “ischemic” electrocardiographic changes during adenosine infusion, redistribution of flow from the endocardium toward the epicardium or coronary steal may be a contributing factor.

Other important hemodynamic effects observed by Ogilby and coworkers, such as a substantial increase in cardiac output (average of 59% in normal subjects and 40.6% in coronary patients) and a decrease in peripheral vascular resistance (average of 35% in normal subjects and 42% in coronary patients), can be explained by the systemic vasodilatory effect of adenosine. This relatively mild systemic vasodilation is in stark contrast with the much more pronounced coronary vasodilatory effect of adenosine, which increases the coronary blood flow fourfold to fivefold.

Apart from these interesting hemodynamic effects of adenosine, the inability of Ogilby and coworkers to demonstrate adenosine-induced wall motion abnormality in most patients who did demonstrate transient perfusion defects remains an important observation with an immediate practical consequence, because it would argue against using radionuclide angiography or echocardiography in association with adenosine with the aim of diagnosing coronary artery disease noninvasively. Consistent with their present observations, the authors had previously reported a low frequency of adenosine-induced wall motion abnormalities by twodimensional echocardiography in patients who had a high prevalence of adenosine-induced transient perfusion defects. A low sensitivity of vasodilator-induced wall motion abnormality had previously been predicted in the basis of experimental studies.

In contrast with the above findings, Zoghbi et al have reported a high sensitivity (85%) and specificity (92%) for coronary artery disease detection using adenosine two-dimensional digital echocardiography. The sensitivity, however, was lower (60%) in patients with normal resting ECGs. Other recent preliminary echocardiographic reports in abstract form seem to indicate that adenosine-induced wall motion abnormalities occur often in coronary artery disease patients. It is quite possible, although unproven, that patient selection may account for some of these differences. Thus, patients with multivessel disease, and especially those with well-developed collateral circulation, may be more prone to developing true myocardial ischemia during adenosine administration, which could lead to wall motion abnormalities. Germane to this issue, Picano et al had previously reported a moderate sensitivity (74%) for coronary artery disease detection by two-dimensional echocardiography during high-dose dipyridamole infusion. In fact, dipyridamole echocardiography is widely used in Europe, although it has not been a very popular test among US echocardiographers.

Hence, more information from large numbers of patients is clearly needed before the eventual diagnostic role of adenosine two-dimensional echocardiography is determined. Pivotal to resolving this controversy would be the use of blind readings and quantitative analysis of regional wall motion by echocardiography to minimize observer biases during a purely visual image interpret-
tion, as is ordinarily done today. Until this information is forthcoming, one would be well served to continue to use myocardial perfusion scintigraphy as the preferred imaging modality during pharmacological vasodilation, because the diagnosis of coronary artery disease by perfusion imaging does not require the presence of ischemia, whereas echocardiography relies on the demonstration of wall motion abnormality secondary to ischemia, which may be provoked by adenosine in some patients with coronary disease but probably not in most.

References
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