Adenosine Myocardial Perfusion Imaging

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Adenosine myocardial perfusion imaging is useful in diagnosis of coronary artery disease (CAD) and risk assessment in patients who have exercise limitations. As a pharmacologic stressor, adenosine acts on two cell-surface purine receptors, A1 and A2. Activation of A2 receptors cause coronary vasodilation. Unlike other pharmacologic stressors, such as dipyridamole and dobutamine, adenosine is an endogenous biochemical. Adenosine perfusion studies have a relatively high sensitivity and specificity (80%–90%) for identifying CAD. Images from adenosine studies are comparable to, or better than, images from exercise myocardial perfusion studies. The side effects are common, but not serious; they are short-lived and rarely require the administration of aminophylline.

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Myocardial perfusion imaging with radiotracers depends on stressing the heart, usually with exercise but in some cases with a pharmacologic stressor. Four pharmacologic stress agents have been evaluated clinically: dipyridamole, adenosine, dobutamine and arbutamine. Dipyridamole (Persantine®, DuPont) and adenosine (Adenocard®, Fujisawa) are the only agents approved by the U.S. Food and Drug Administration for use in pharmacologic stress perfusion imaging.

Adenosine is the only stress agent that is also endogenously produced (*1*). Vascular and myocardial cells produce adenosine through two pathways: the adenosine triphosphate (ATP) and S-adenosylmethionine cycles (*1,2*). The parent compound, ATP, has also been used recently as a pharmacologic stressor for myocardial perfusion studies.

Once produced, adenosine leaves the cell and acts on surface purine receptors A1 and A2. Adenosine then returns to the cell and is metabolized quickly to ATP or uric acid. This is a very active and fast pathway; the biologic half-life of adenosine is <1.0 sec. Activation of A2 receptors results in vasodilation, whereas activation of A1 receptors may cause atrioventricular block.

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IMAGING PROTOCOL

The early protocols called for a titration of the adenosine dose (*3*). Most laboratories today use the standard dose of 140 μg/kg/min for 6 min, which produces a consistent hyperemic response (*3,4*). For unstable patients, it is still appropriate to titrate the adenosine until the maximal dose is reached.

The radiotracer is injected during adenosine infusion (at 3 min of a 6-min infusion protocol), not postinfusion (as with dipyridamole). Because adenosine produces maximal hyperemia, ancillary exercise studies are not necessary. Also, in our experience with single-photon emission computed tomography (SPECT), splanchnic uptake does not interfere with image interpretation.

The exact mechanism of adenosine's vasodilatory effect is not completely understood. Vasodilation is a complex process that may involve changes in cyclic adenosine monophosphate (AMP), cyclic quanosine monophosphate (GMP), calcium release, calcium uptake or endothelial relaxing factor (*2*). There may be a biofeedback mechanism that triggers a signal regulating adenosine release in response to changes in the ratio of myocardial oxygen supply and demand (*5*). This signal prompts adenosine levels to increase or decrease, restoring the supply-demand balance.

Adenosine is now also given directly into the coronary arteries during cardiac catheterization to produce vasodilation and hyperemia. The pharmacologic effect is extremely rapid, faster than that of dipyridamole, which acts by increasing endogenous adenosine concentrations (by blocking the reuptake mechanism).

Bolus injection of adenosine is used to break supraventricular arrhythmias. In the future, it may be possible to develop a pure agonist to trigger a more precise pharmacologic effect, or to combine adenosine with an A1 antagonist to eliminate some of the side effects.

Contraindications to pharmacologic stress-testing with adenosine are similar to those of dipyridamole infusion, as discussed elsewhere in this section by Leppo ["Dipyridamole Myocardial Perfusion Imaging"]. As with dipyridamole, methyl-xanthine medication and caffeine consumption should be discontinued, preferably 24 hr prior to adenosine testing. In addition, in patients who are taking dipyridam-

ole as a medication, it should be withheld for at least 12 hr before adenosine testing because dipyridamole significantly potentiates the effects (and side effects) of the infused adenosine by blocking its reabsorption and metabolism and raising its blood levels.

Clinical Considerations

Wilson et al. measured coronary flow responses to adenosine (*4*). A dose of 140 μg/kg/min produced a response comparable to that of papaverine, which is the gold standard to assess coronary flow reserve. Even at half the clinically recommended dose, adenosine produces a considerable hyperemic response, resulting in a three- to fourfold increase in coronary blood flow. This point is important to remember because, even when the dose is downtitrated, the drug is still producing a strong hyperemic response.

In general, adenosine increases heart rate by 10 to 15 bpm and decreases systolic blood pressure by 10 to 15 mmHg (*1–3,6,7*). Adenosine produces an increase in regional blood flow in all organs except the kidneys, where it causes a decrease in renal blood flow. The increase in cardiac output averages only 50%. The difference in the degree of augmentation of coronary blood flow and cardiac output determines the amount of radiotracer uptake in the myocardium, and provides an explanation for the high-quality perfusion images.

The decrease in blood pressure associated with adenosine (or dipyridamole) infusion is caused by a decrease in systemic vascular resistance, not by depression of left-ventricular function (*6*). The physiologic implications are different, therefore, from the drop in systolic blood pressure during exercise. Compared with the slight increase in cardiac output, the decrease in systemic vascular resistance is greater, resulting in a decrease in systolic blood pressure. The degree of change in output and systemic vascular resistance is similar in normal subjects and in patients with CAD (*6*).

SAFETY AND ADVERSE EFFECTS

From the multicenter registry of nearly 10,000 patients who have undergone adenosine myocardial perfusion studies, the three most common adverse effects are flushing, shortness of breath and chest pain; an estimated 70%–80% of patients experience one or more of these reactions (*8*). The vast majority of these adverse reactions are transient and rarely require a counteracting response.

Interestingly, older patients tolerate adenosine better than younger patients. With respect to gender differences, all adverse effects are more common in women than in men, with the exception of flushing.

The adverse effect that has generated the most attention, a high degree of atrioventricular block, has been reported in <1% of patients (*8*). In general, it occurs during the first 2–3 min of adenosine infusion and is transient. First-degree block (prolongation of PR interval) is more common, occurring in 10% of patients. Second-degree block occurs in 4%–5% of patients. The effect on A-V nodes often occurs after the effect on coronary blood flow. Therefore, the radiotracer should be injected at the time of A-V block; then, the dose of adenosine is down-titrated or discontinued, depending on the hemodynamic condition of the patient (*9*).

EFFICACY

Measurement of myocardial blood flow with nitrogen-13 ammonia showed that the degree of coronary hyperemia by adenosine was comparable to that of dipyridamole, approximately 4.5 times baseline blood flow (*10*). Dobutamine infusion increased blood flow by 3.0 times. Dobutamine's mechanism of action is similar to that of exercise; the increase in flow is due to increase in demand. The effects of adenosine and dipyridamole are direct vasodilation, resulting in higher coronary blood flow responses.

In the early clinical studies by Verani et al., adenosine-thallium imaging provided an overall sensitivity of 90% for detection of CAD (*3*). The sensitivity was higher in patients with multivessel disease than in patients with single-vessel disease. Other studies have produced similar results. For example, Gupta et al. found a sensitivity of 85% and a specificity of 80% (*14*). Interestingly, the specificity with dipyridamole-thallium imaging is also reported in the 80% to 90% range (*2*). In general, specificity results reported with pharmacologic stressor appear to be significantly higher than those reported with exercise (*2*). This difference, however, may be due to less patient referral bias in the former studies.

Clinical Observations

There are two caveats to keep in mind when analyzing these study results. Perfusion defects may be detected in territories of "mild" coronary stenosis and "occluded" but collateralized vessels. Such patients may not require intervention unless they are symptomatic.

In our experience, three indicators were useful to identify high-risk patients (those with three-vessel or left-main disease) (*15*): (1) the presence of multivessel perfusion abnormality, (2) increased ^{201}Tl uptake in the lung and (3) ST-segment depression. Nishimura et al. have shown three factors to be predictive of ST-segment depression during adenosine infusion (*12*): (1) presence of collaterals on angiography, (2) angina during adenosine infusion and (3) low systolic blood pressure at baseline. The presence of collaterals, however, was the most important factor.

CONCLUSION

Adenosine myocardial perfusion imaging is useful in evaluating patients with CAD who cannot exercise. A review of clinical trials indicates that adenosine perfusion studies provide high sensitivity and specificity (80%–90%) for identifying CAD. Images from adenosine studies are comparable to, or better than, images from exercise myocardial perfusion studies.

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