Adenosine echocardiography in the diagnosis of coronary artery disease

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Adenosine is a naturally occurring vasodilator which has been used for the induction of maximal coronary hyperaemia in the cardiac catheterization laboratory and in conjunction with myocardial perfusion scintigraphy. Its use as a stress agent with echocardiography is dependent upon the development of coronary steal. The sensitivity of adenosine stress echocardiography has been reported to be quite variable, depending on the nature of the population studied. However, in individuals without previous myocardial infarction, the test has a poor sensitivity, particularly in patients with single vessel coronary disease. Moreover, although the agent is safe, troublesome side effects are frequent. The combination of lower sensitivity than competing techniques, side effects, and cost do not favour the combination of adenosine stress with echocardiography.

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Mechanism of action

Adenosine is a powerful, naturally occurring vasodilator, which controls the homeostatic responses of the microvasculature. The mechanism of action and metabolism of this agent are illustrated in Fig. 1. After the adenosine receptor is activated, cyclic AMP is released, which leads to reduction of calcium uptake, potassium channel stimulation and smooth muscle relaxation. Sympathetic neurotransmission may also be influenced by adenosine receptor activation.

The attachment of adenosine to the receptor is blocked by xanthine-containing compounds, including theophylline and caffeine. Extracellular adenosine is rapidly and actively transported into the cell, where it is rapidly metabolized by adenosine deaminase and other pathways. Both the uptake into the cell and subsequent metabolism are inhibited by dipyridamole and papaverine. These insights into the mechanism of action and metabolism of adenosine have important implications for its use in stress testing. First, it is important that patients abstain from xanthine-containing compounds before the test. Specifically, both standard and decaffeinated coffees should be avoided for at least 24 h. Second, patients taking dipyridamole for other reasons who are administered adenosine may have the effects of the adenosine potentiated by dipyridamole. Finally, because of the direct action of adenosine, the onset and offset of adenosine stress are very rapid, in comparison with dipyridamole, which acts indirectly by increasing endogenous adenosine levels through reduction of cell uptake and destruction.

The use of adenosine for stress testing is dependent on its effects as a coronary vasodilator. In combination with invasive measurements of coronary blood flow velocity by Doppler, or non-invasive measurements of myocardial perfusion using perfusion imaging, coronary artery disease is identified by failure to attain maximal coronary vasodilation in areas with flow-limiting coronary stenoses. In contrast, in combination with echocardiography, there is a need for stress to induce ischaemia in a metabolic and functional sense. This occurs through the mechanism of coronary steal, discussed by Picano and Lattanzi.

Clinical effects of adenosine administrations

Several invasive studies in the early 1990s indicated the efficacy of adenosine as a coronary vasodilator. In patients largely without significant coronary disease, Wilson et al. showed that increasing doses of adenosine to 0.14 μg·kg⁻¹·min⁻¹ increased coronary blood flow velocity reserve to four times normal, a level comparable to that attainable with papaverine, the usual vasodilator for this purpose. The use of adenosine rather than papaverine has the benefit of avoiding QT prolongation and arrhythmias which may occur with the latter agent. In patients with coronary disease, Kern et al. showed...
that the vasodilator response to adenosine was blunted, in parallel to reduction of the vasodilator response to papaverine (Fig. 2). In a comparison of the degree of coronary blood flow increase with vasodilators, Rosen et al.\textsuperscript{3} demonstrated that adenosine and dipyridamole produce comparable levels of augmentation of coronary blood flow, although both were significantly less than that inducible with papaverine. As papaverine is suitable only for use in the angiography laboratory, the important features of these findings are that for the purpose of stress testing, adenosine has a similar effect to that obtainable with papaverine, and that it is comparable with dipyridamole. However, the benefit of adenosine in comparison with dipyridamole is its reproducibly short onset of action, in comparison with the delayed onset of dipyridamole, maximum vasodilation due to which may vary from 4 to 14 min after administration of the stress.\textsuperscript{7}

The haemodynamic response to adenosine and dipyridamole is variable between patients, and the systemic haemodynamic response correlates poorly with the degree of augmentation of coronary blood flow. At a dose of 0.14 µg kg\textsuperscript{-1} min\textsuperscript{-1}, systemic haemodynamic changes generally occur at doses >100 µg kg\textsuperscript{-1} min\textsuperscript{-1}, and involve a reduction of systolic and diastolic blood pressure, usually by about
effects may be very intense (Table 2). The most common

dyspnoea, flushing and headache. In contrast, while
dipyridamole causes fewer side-effects\[14\], these last
longer and hence may be more of a problem for

management.

The use of adenosine stress is contraindicated in
patients with a history of bronchospasm, those taking
methylxanthine or dipyridamole (see above) and in
patients with a borderline blood pressure. Because of
concern about high grade atrioventricular block, caution
should be used in studying patients with untreated
atrioventricular block.

### Adenosine scintigraphy

Several large studies of adenosine stress perfusion
imaging\[8,15-17\] were published in the early part of this
decade (Table 3). These reports showed the sensitivity of
adenosine stress thallium SPECT to vary from 83–92%,
with a sensitivity of 73–87% in patients with single-vessel
disease, and 82–91% in patients without prior myocar-
dial infarction. In these series, the specificity of
adenosine stress was in the range of 90%. In patients
with left bundle branch block, avoidance of stress-
induced tachycardia may reduce false-positive scans,
and this may be a particular benefit of adenosine stress
perfusion imaging\[18\].

Adenosine stress produces comparable results to those
obtainable with exercise\[19,20\], and in patients
who are unable to exercise, adenosine is an effective
alternative to dipyridamole stress testing for myocardial
perfusion imaging. Because of the problems of dipyrida-
 mole non-responsiveness, it may even be more effective
than dipyridamole stress testing in some patients.
Unfortunately, however, not all centres report the levels of
specificity for perfusion imaging described in this series,
and undoubtedly this is an expensive test for the identifi-
cation of coronary disease. The use of adenosine with
other techniques has therefore been examined.

### Adenosine stress echocardiography

Studies summarizing the accuracy of adenosine stress
echocardiography for the identification of coronary dis-
ease are summarized in Table 4\[21-25\]. These data show a
striking heterogeneity in the results reported, generally
using 0-14 μg·kg⁻¹·min⁻¹ of adenosine over 6 min.

### Side effects

Although adenosine stress has been shown to be safe in
studies of more than 15 000 patients, side effects occur in
about 80% of patients. The frequency of ischaemia and
major side effects in selected large studies are sum-
morized in Table 1\[9-11\]. Chest pain occurs in 20–30% of
patients, and ST depression in about 10% of patients.
Myocardial infarction provoked by adenosine stress has
been reported in less than 1 in 10 000 patients, and
bronchospasm occurs in 1 in 1000 patients. High
grade atrial ventricular block, which is usually transient
and well tolerated\[12\], has been reported with variable
frequency in different studies, in up to 6% of patients.

Minor side effects are very common\[9,11,13\], and
often not well tolerated by patients. The onset of the
vasodilator effect of adenosine is rapid, and these side
effects may be very intense (Table 2). The most common

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>1VD</th>
<th>Non-MI</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nguyen[6]</td>
<td>92% (n=53)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Verani[8]</td>
<td>83% (n=29)</td>
<td>73% (n=15)</td>
<td>—</td>
</tr>
<tr>
<td>Nishimura[17]</td>
<td>87% (n=70)</td>
<td>81% (n=32)</td>
<td>82% (n=45)</td>
</tr>
<tr>
<td>Iskandrian[19]</td>
<td>92% (n=132)</td>
<td>87% (n=54)</td>
<td>91% (n=95)</td>
</tr>
</tbody>
</table>

1VD = one vessel disease.
Table 4  Accuracy of adenosine stress echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (n)</th>
<th>Specificity (n)</th>
<th>Dose/time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoghbi[221]</td>
<td>85% (n=60)</td>
<td>92% (n=13)</td>
<td>To 0:14/7 min</td>
</tr>
<tr>
<td>Martin[211]</td>
<td>40% (n=25)</td>
<td>93% (n=15)</td>
<td>0:14/6 min</td>
</tr>
<tr>
<td>Marwick[231]</td>
<td>58% (n=59)</td>
<td>87% (n=38)</td>
<td>To 0:18/7 min</td>
</tr>
<tr>
<td>Amanullah[241]</td>
<td>74% (n=34)</td>
<td>100% (n=6)</td>
<td>0:14/6 min</td>
</tr>
<tr>
<td>Heinle[251]</td>
<td>56% (n=16)</td>
<td>—</td>
<td>0:14/6 min</td>
</tr>
</tbody>
</table>

Figure 4  Influence of previous myocardial infarction (hence abnormal resting ECG) on sensitivity. Modified from Zoghbi[221].

While the test is highly specific, the sensitivity has varied between 40% and 85%. The reasons for this are illustrated in Fig. 4; inclusion of all patients with and without myocardial infarction is associated with a high sensitivity for adenosine echocardiography, largely because of the presence of resting wall motion abnormalities in patients with prior infarctions. However, in individuals with normal electrocardiograms, without prior infarction, the sensitivity overall was 60%, and in single-vessel disease was only 30%. This figure illustrates the importance of using a population suffering from ischaemia rather than infarction to document the efficacy of a stress test.

Comparison of adenosine echocardiography with other tests

In a small study Ogilby et al.[26] suggested that myocardial perfusion imaging was more sensitive that echocardiography in combination with adenosine stress. As a result of the heterogeneity in the reported studies, Marwick et al.[23] performed a trial of 97 patients studied with adenosine echocardiography and MIBI SPECT, together with dobutamine echocardiography and MIBI SPECT. The stress tests were administered over a 3-day period, at which time the patient presented for angiography, and echocardiography and nuclear stress testing were performed simultaneously. Patients with myocardial infarction were excluded to avoid spurious augmentation of the results for sensitivity.

Figure 5  Comparative side-effects of adenosine and dobutamine stress[23].

The side effects of dobutamine and adenosine stress are summarized in Fig. 5. Using both dobutamine and adenosine, the test was terminated because of ischaemia or the conclusion of the protocol in about one-third of the patients. In the remainder, who had the test terminated early due to side effects or complications, the commonest problems with dobutamine were hypotension and arrhythmias. In contrast to these physician-driven causes of test termination, patient symptoms (in particular dyspnoea and hypotension) were a more common cause of premature cessation of the adenosine test. With reference to the haemodynamic responses to dobutamine and adenosine, dobutamine induced a greater peak heart rate, systolic blood pressure and rate pressure product.

Neither ST segment depression nor angina were sensitive indices of coronary artery disease in patients studied with either adenosine or dobutamine. In contrast, adenosine stress perfusion scintigraphy and both dobutamine echocardiography and perfusion scintigraphy were sensitive indicators of the presence of significant disease, and were significantly more sensitive than adenosine echocardiography (Fig. 6). The specificities of these techniques were comparable, although there was a trend for the perfusion imaging techniques to be less specific than the echocardiographic techniques. The lower sensitivity of adenosine echocardiography than dobutamine echocardiography or either scintigraphic
approaches was apparent in patients with both single- and multivessel disease. These findings have been confirmed by subsequent studies by Amanullah et al.\[11\], who showed the sensitivity of adenosine echo to be 74% in comparison with 94% with adenosine thallium SPECT, and Heinle et al.\[12\], who showed the sensitivity of adenosine echo to be 56%, in comparison with 69% for perfusion imaging.

Finally, in our experience, and that of Martin et al.\[13\], patients dislike adenosine stress. Of 40 patients administered dobutamine, dipyridamole, and adenosine, dobutamine was the preferred agent in 50%, dipyridamole the preferred agent in 40%, and adenosine was preferred in approximately 10%. The cost of these drugs for stress testing in the U.S.A. is currently $179.00 for adenosine, $95.00 for dipyridamole, and $1.00 for dobutamine.

**Conclusions**

In patients who are unable to exercise, dobutamine is preferable to adenosine stress if echocardiography is to be performed. If perfusion imaging is to be performed, the techniques appear to be comparable, although vasodilator stress perfusion imaging is certainly more established, and possibly slightly more sensitive. Adenosine is a relatively ineffective stress for echocardiography, particularly in patients with single-vessel disease. This may also be true but to a lesser extent for dipyridamole; the latter test has proven prognostic value, which has not been established for adenosine stress testing. Currently, the test is expensive and unpopular with patients because although it is safe, side effects are frequent. The use of adenosine for pharmacological stress echocardiography cannot be recommended on the basis of the current literature.


