# Vasodilator stress agents for myocardial perfusion imaging

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In this issue of the *Journal*, Yao et al report on the prognostic value of adenosine triphosphate (ATP) myocardial perfusion imaging (MPI) with Technetium-99 sestamibi (Tc-99m) in a population aged 70 years and older.[1] The ability to exercise in this population is expected to be rather limited. A total of 415 patients with suspected coronary artery disease (CAD) were identified and retrospectively enrolled in the study. The primary composite end point was major adverse cardiac events (MACE) and included death from a cardiac etiology, nonfatal myocardial infarction (MI), and late coronary revascularization (>60 days). Sixteen patients met exclusion criteria as they underwent early coronary revascularization ≤60 days after MPI. Reversible and/or fixed perfusion defects were considered abnormal and patients were followed over a mean of 3.45 ± 1.71 years. MACE occurred in 37 patients, including 9 cardiac deaths, and was significantly lower in patients with normal MPI, even after adjusting for other variables such as age >80 years, male gender, chest pain or dyspnea, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease, atrial fibrillation, and abnormal ATP stress ECG. Each of the individual outcomes included in MACE was also significantly lower in patients with normal MPI. In addition, although patients aged ≥80 years had higher MACE rates than those aged 70-79 years when the summed stress score (SSS) was >8, the two groups had similar MACE rates when the SSS was ≤8. These results confirm the prognostic value of ATP-MPI in an elderly population with suspected CAD.

The proportion of pharmacologic stress tests performed in the United States has steadily increased over the past several decades. Exercise stress testing is favored over vasodilator stress, since it is more physiological and since it assesses the functional capacity which provides important prognostic information.[2] However, when patients are not able to achieve a specified gender and age-adjusted target heart rate and exercise capacity, the test loses some of its diagnostic and prognostic value. Further, a significant proportion of the population in developed countries is unable to exercise. This is likely the primary driver of the 23% drop in the rates of exercise stress tests in 2006-2009 as compared to 1991-1995.[3] In these instances, and in other special circumstances, such as the presence of left bundle branch block or ventricular paced rhythm, pharmacologic stress agents are used for myocardial perfusion imaging. Pharmacologic stress agents currently in use fall under two categories: the inotropes/chronotropes that trigger a stress response by increasing myocardial oxygen demand, and the vasodilator agents that primarily trigger coronary vasodilation.[4] The former include dobutamine, arbutamine, and higenamine, a β-receptor agonist derived from a traditional Chinese medicine which is currently undergoing clinical trials in China. The latter, which will be the focus of our discussion, include dipyridamole, adenosine, adenosine triphosphate (ATP) and regadenoson (Table 1). Of the vasodilator agents mentioned, ATP, the pharmacologic stress agent used in the study by Yao et al,[1] is not approved for use in the United States but is being used in other parts of the world including Japan and China.

The currently used vasodilator stress agents all mediate their effects, either directly or indirectly,

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**Table 1.** Vasodilator stress agents

| | Standard protocol | Timing of radiotracer injection | Half-life | Elimination | Receptor activity | Side effects |
|---|---|---|---|---|---|---|
| Dipyridamole | 0.56 mg·kg$^{-1}$ intravenously over 4 minutes | 7 minutes after beginning of infusion | 30-45 minutes | Hepatic clearance | Nonselective adenosine receptor agonist | ++++ |
| Adenosine | 140 mcg·kg$^{-1}$·minute$^{-1}$ intravenously for 6 minutes | At least 2 minutes into infusion, infusion to continue for at least 2 minutes after radiotracer injection | About 1 second | Cellular uptake | Nonselective adenosine receptor agonist | +++ |
| Adenosine triphosphate | 160 mcg·kg$^{-1}$·minute$^{-1}$ intravenously for 5 minutes | 3 minutes into infusion, infusion to continue for at least 2 minutes after radiotracer injection | Less than 20 seconds | Cellular uptake | Nonselective adenosine receptor agonist + P2$\gamma$-purinergic receptor agonist | ++/+++ |
| Regadenoson | 400 mcg intravenous bolus | 10-20 seconds after regadenoson bolus | 33-108 minutes | Renal clearance | Selective A2A adenosine receptor agonist | + |

through activation of adenosine receptors. Adenosine is an endogenous extracellular signaling molecule that plays an important regulatory role in the human body. It also constitutes the nucleoside base of both ATP and cyclic adenosine monophosphate. In addition to its vasodilatory effects, adenosine has antithrombotic properties, regulates sympathetic activity, and affects systolic blood pressure and heart rate, decreasing the former by 10-15 mm Hg and increasing the latter by 10-15 bpm.[5] Its ubiquitous physiologic functions are mediated through its different receptors: A1, A2A, A2B, and A3. A2A and A2B activation results in vasodilation of most vascular beds with the exception of the renal bed[5] thereby increasing perfusion to all organs except for the kidneys. A1 receptors mediate the negative chronotropic and dromotropic effects of adenosine on the heart, while A3 receptors mediate mast cell degranulation and bronchial constriction.[5]

Dipyridamole, a pyrimidine base, exerts it vasodilatory properties indirectly by inhibiting the cellular reuptake and deamination of adenosine. The nonselective binding of adenosine to its A2A receptor in the coronary vascular bed induces hyperemia, and thus dipyridamole can produce a fourfold increase in coronary flow to generate a significant flow gradient distal to a coronary stenosis.[6] Dipyridamole is infused intravenously at a dose of 0.56 $mg \cdot kg^{-1}$ over 4 minutes. The radiotracer is then injected at 7 minutes (peak vasodilation).[7] In a registry of 3,911 patients, Ranhosky et al describe the incidence of side effects with dipyridamole in the setting of stress testing. A total of 1820 (46.5%) had minor adverse effects, including chest pain (19.7%), headache (12.2%), dizziness (11.8%), nausea (4.6%), and flushing (3.4%). On the other hand, 10 (0.26%) had major adverse events, 2 had fatal MI, 2 nonfatal MI, and 6 developed acute bronchospasm.[8]

Despite the early understanding of the adenosine-mediated vasodilatory effect of dipyridamole, there was initial reluctance toward the direct use of adenosine infusion for MPI, mainly due to concerns stemming from its known atrioventricular (AV) blocking properties. When Wilson et al demonstrated the safety of infusing relatively low doses of intravenous adenosine (35-140 $\mu g \cdot kg^{-1} \cdot minute^{-1}$),[9] the superiority of this approach was quickly appreciated, especially with the much shorter half-life of adenosine as compared to dipyridamole. Adenosine is infused at rate of 140 $\mu g \cdot kg^{-1} \cdot minute^{-1}$ over 4-6 minutes with tracer injection at least at 2 minutes with the infusion continuing for at least 2 minutes after tracer injection.[7] Using this infusion rate, adenosine has been shown to increase human coronary blood flow fourfold.[7] Adenosine use as a stress agent for MPI was approved by the Food and Drug Administration (FDA) in 1990 and its utilization quickly grew. The Adenoscan study, which included more than 9000 patients from a multicenter registry, confirmed the safety and tolerability of intravenous adenosine infusion in the setting of MPI.[10] In this registry, the reported incidence of side effects was 81%. The most common were flushing (36.5%), dyspnea (35.2%), chest pain (34.6%), gastrointestinal discomfort (14%), and headache (11%). Supraventricular and ventricular arrhythmias were experienced by 3.3% of patients and AV block by 7.6%. Bradycardia was described in 0.2%, bronchospasm in 0.1%, pulmonary edema in 1 patient, and MI in one patient who had coronary angioplasty that was complicated by a severe circumferential dissection 3 days prior to adenosine stress testing. There were no deaths.[10]

ATP, a precursor to adenosine, is expected to produce an equivalent hyperemic response to adenosine with a longer half-life.[11] ATP is rapidly metabolized into adenosine diphosphate, then into adenosine monophosphate and subsequently adenosine. This confers ATP a half-life of about 20 seconds as compared to the adenosine half-life of approximately 1 second. Yonezawa et al demonstrated that an ATP infusion rate greater than 0.15 $mg \cdot kg^{-1} \cdot minute^{-1}$ results in maximal hyperemia in the coronary circulation.[12] The current protocol recommends an ATP infusion of 0.15 $mg \cdot kg^{-1} \cdot minute^{-1}$ over 5 minutes. Similarly to adenosine, the tracer is injected 3 minutes after infusion initiation. ATP is thought to be able to induce vasodilation through two different mechanisms. The first is endothelium dependent, and is the result of ATP binding to P2$\gamma$-purinergic receptors. The second is through its action on the adenosine A2A receptor (either directly, or via its degradation products adenosine 5′-monophosphate and adenosine).[13] The diagnostic equivalence of an intravenous infusion of ATP vs adenosine for MPI was demonstrated in a study by Miyagawa et al, where all patients underwent coronary angiography after stress testing, and in which the sensitivity and specificity for detection of CAD were 88% and 80%, respectively, by visual analysis, and 91% and 86% by computer quantification.[14] In an interesting study by Ohba et al, a small group of patients (n = 17) known to have CAD by coronary angiography, underwent exercise and ATP within 60 days of angiography. The two stress modalities were equivalent in detecting single vessel disease. However, patients with multi-vessel disease were found to have more extensive and severe ischemia on MPI with ATP than with exercise. This may be related to the different levels of intensity of exercise required to induce ischemia in different regions of the myocardium. Hence, a patient may develop symptoms of ischemia along with ECG changes during exercise, resulting in termination of the stress test prior to the development of ischemia in other areas.[15]

The side effects reported with ATP are similar to those reported with adenosine and dipyridamole. While the frequency of side effects with ATP was lower than those reported with adenosine in some studies,[14] more recent studies show a rate of side effects with ATP that is similar to those reported in the Adenoscan registry.[16] In the study by Miyagawa et al,[14] the frequency of experienced side effects with ATP was significantly lower in men than in women (46% vs 66%). Dyspnea (8%), headache (7%), flushing (6%), epigastric discomfort (4%), and sore throat (4%) were among the most common side effects described. There were no instances of death, acute MIs, or ventricular arrhythmias. Eighty percent of the symptoms were reported to be mild; however, the severity was graded by the investigators rather than the patients. A total of 6 patients (2%) experienced asymptomatic AV block, divided equally between 1st and 2nd degree blocks. The blocks spontaneously resolved within a minute of ATP infusion termination. There were no instances of complete AV block. In comparison, AV block followed adenosine infusion in 7.6% of patients in the Adenoscan registry.[10] In an abstract very recently published by Tang, 116 of 136 patients (85.29%) had side effects. Chest pain was reported by 60.29%, dyspnea by 55.88%, and dyspnea by 38.24% of patients. The severity of the symptoms was not reported and there was no mention of myocardial infarction, bronchospasm, and AV block.[16] This smaller incidence of adverse events with ATP as compared to adenosine may be the basis of its more frequent use in some countries. It is important to note, however, that these studies did not directly compare ATP to adenosine, and therefore any conclusion regarding side effect profiles is preliminary and will need to be verified in larger head-to-head studies.

The tendency of vasodilator agents to cause a variety of side effects generated an interest in the development of new agents that would selectively bind the adenosine A2A receptor, thereby theoretically decreasing the occurrence of side effects including AV block (mediated by A1 receptors) and bronchospasm (mediated by A2B receptors). In the beginning of the 21st century, a new class of selective A2A receptor agonists emerged.[17] Regadenoson is currently the only selective adenosine receptor agonist with FDA approval (received on April 10th 2008). Whether regadenoson's metabolism is influenced by endogenous enzymatic reactions is still unclear. A prospective study showed a more pronounced increase in systolic blood pressure after regadenoson injection in patients with a common adenosine monophosphate deaminase-1 (AMPD1) polymorphism, present in about 20% of the population. The polymorphism results in reduced AMPD1 function that normally plays a key role in the purine salvage cycle of adenosine in order to regenerate energy stores in states of ischemia.[18] Many of regadenoson's properties make it better suited for vasodilator stress testing than the nonselective agents. Its affinity to the A2A receptor is higher than that of adenosine. This allows regadenoson to have a very short half-life while still able to achieve maximal coronary vasodilation with the presence of a large A2A receptor reserve.[19] Regadenoson is given as a single, fixed, weight-unadjusted 400 μg bolus thus simplifying the stress protocol. It has a rapid onset of action and it is easily reversible with an antagonist (aminophylline).[17] The radionuclide tracer is injected 10-20 seconds after the regadenoson injection.[7]

The diagnostic equivalence of regadenoson MPI to adenosine MPI was demonstrated in the ADVANCE MPI 2 trial which randomized 784 patients at 54 different sites in a double-blind fashion to undergo regadenoson vs adenosine MPI in a 2:1 ratio within 4 weeks of an initial adenosine MPI study.[20] The results of the ADVANCE MPI 2 trial were described by Iskandrian et al and showed an agreement rate of 0.63 ± 0.03 for regadenoson-adenosine and 0.64 ± 0.04 for adenosine-adenosine.[20] Similar results were described by Cerqueira et al when both ADVANCE MPI 1 and 2 populations were combined (total of 1871 patients) and showed an adenosine-adenosine agreement rate of 0.62 ± 0.03 and adenosine-regadenoson agreement rate of 0.63 ± 0.02.[21] Mahmarian et al showed better agreement rates using automated quantitative analysis with a difference of −0.13 ± 4.2% in the serial adenosine group and −0.03 ± 3.9% in the adenosine-regadenoson group.[22] Recent studies have reported on the prognostic value of regadenoson MPI.[23-25] In the ADVANCE MPI trials, regadenoson had better side effect profile and tolerability than adenosine. The side effects were mostly reported as mild in intensity, with an incidence equivalent to or less than adenosine. The incidences of flushing (24% vs 17%), chest discomfort (16% vs 11%), and chest pain (13% vs 8%) were at the advantage of regadenoson. Notable exceptions that had higher rates with regadenoson were headache (16% vs 29%) and gastrointestinal discomfort (2% vs 6%). A summed symptom score, which was calculated based on the presence and severity of flushing, dyspnea, and chest pain, was significantly lower with regadenoson (0.9 ± 0.05 vs 1.1 ± 0.08) ($P = .013$).[20] The incidence of second-degree AV block was also lower, with no occurrences in the regadenoson group compared to 3 occurrences in the adenosine group ($P = .043$).[20] More recent reports have described instances of asystole,[26] high-degree AV block, MI, cerebrovascular accidents, and seizures with regadenoson,[27,28] prompting an FDA warning against using regadenoson in patients with signs or symptoms of myocardial ischemia. The issue of

serious complications encountered during stress testing using the different stress modalities has been recently reviewed in the *Journal.*[29]

Currently, regadenoson is by far the most commonly used pharmacologic agent in the United States, accounting for 84% of the pharmacological stress tests in 2013.[30] Other, nonselective agents, continue to be widely used in other countries. It will be interesting to follow the change in trend of vasodilators used after the initiation of regadenoson use in Europe.

## Disclosure

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