Regadenoson Cardiac Stress Myocardial Perfusion Scintigraphy

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Review

Regadenoson (Lexiscan™) is a pharmacologic cardiac stress test agent that results in coronary artery vasodilation. Healthy coronary arteries dilate, whereas arteries with extensive atherosclerosis or coronary spasm do not. Patient with microvascular disease also have decreased vascular dilation in response to regadenoson. The result is an alteration in coronary blood flow, with a relative decrease in flow to vascular territories distal to diseased vessels and a relative increase in flow to vascular territories served by healthy vessels. This alteration in blood flow is detected on a molecular level by nuclear myocardial perfusion imaging. Patients with extensive disease may have normal myocardial perfusion at rest because the alteration in blood flow is not pronounced.

When there is a significant alteration in myocardial blood flow during stress, but normal blood flow at rest, the patient is demonstrating inducible myocardial ischemia, and is at an increased risk of adverse cardiac events.

Patients with normal or near normal perfusion during cardiac stress do best with risk reduction and medical therapy, whereas patients with evidence of inducible ischemia affecting about 10% or more of the left ventricle have a mortality benefit from revascularization. This was first demonstrated by Hachamovitch et al (Circulation. 2003 Jun 17;107(23):2900-7) and subsequently supported by the COURAGE Trial (N Engl J Med. 2007 Apr 12;356(15):1503-16) and by additional work by Hachamovitch et al (Eur Heart J. 2011 Apr;32(8):1012-24).

Hachamovitch's research, published by Circulation in 2003, includes an important figure demonstrating the usefulness of myocardial perfusion scintigraphy in guiding patient therapy. Figure 4 in the manuscript demonstrates that when the % Total Myocardium Ischemic is below about 10%, medical therapy alone is associated with a lower log hazard ratio (greater survival). When the % Total Myocardium Ischemic is above about 10%, revascularization was associated with a survival benefit. As the percentage of ischemic myocardium increased, survival decreased.

Exercise treadmill testing is the preferred method of cardiac stress when performing a stress myocardial perfusion scan, however, it is important that the patient be able to perform adequate stress in order to achieve an acceptable diagnostic accuracy. At low levels of stress, the coronary vasodilation is not stimulated enough to result in an alteration in regional coronary blood flow when diseased vessels are present.

In general, adequate stress is defined as achieving 85% or more of their predicted maximum heart rate [= 0.85 * (220-age)]. Patients with atrial fibrillation or with severe deconditioning may achieve this target heart rate quickly when performing treadmill stress. In these patients, there is some controversy over what defines adequate stress. A rule of thumb is that patients should be able to exercise at least 3 minutes of a Bruce Protocol stress test and achieve 85% of their predicted maximum heart rate. Another metric used is the double product (= heart rate times systolic blood pressure), with a value of 20,000 or greater suggesting that adequate stress has occurred.

Adequate stress can also be defined simply as fatigue, when the purpose of the stress test is to determine a patient's response to medical therapy. In these patients, their cardiac medications are NOT held for the test since the goal is to determine whether or not inducible ischemia occurs when the patient is on their medications.

For patients unable to perform exercise stress testing, pharmacologic stress testing can be used. The three most common agents used in conjunction with myocardial perfusion imaging are dipyridamole, adenosine, and regadenoson. All act by vasodilating the coronary vessels. All require that patients refrain from caffeinated products for a minimum of 12 hours, and ideally for 24 to 48 hours.

To date, research on all three agents have found that they all have a similar side-effect profile, and a similar rate of side-effects. Although there are theoretical benefits for adenosine over dipyridamole (the short half-life) and a theoretical benefit of regadenoson over adenosine (more cardioselective for adenosine receptors), these theoretical benefits have not been shown to decrease side-effects compared to the inexpensive, original agent dipyridamole.

Nevertheless, there are a couple of possible benefits of regadenoson. It is administered as a single rapid bolus, whereas both adenosine and dipyridamole are infused over several minutes. This has important
implications in terms of physician time and patient throughput. In addition, researchers have found that patients subjectively feel better after regadenoson stress compared to after adenosine stress (Iskandrian et al, J Nucl Cardiol. 2007 Sep-Oct;14(5):645-58, Cerqueira et al, JACC Cardiovasc Imaging. 2008 May;1(3):307-16). This “Tolerability Score” was determined by asking patients after stress the simple question, “how do you feel?” After regadenoson stress, 91% of patients responded that they felt comfortable or only slightly uncomfortable, compared to 82% of patients undergoing adenosine stress. To my knowledge, there are no studies that look at patient responses to this question after dipyridamole stress testing. Overall, the rate of any adverse cardiac event after regadenoson is no different than after adenosine, both occurring at a rate of 79% in Iskandrian’s original research. Furthermore, when only looking at severe cardiac events, there also is no difference between adenosine and regadenoson (7% vs 5%, p=0.32). Only when researchers selectively looked at a combined score of just 3 side-effects (flushing, chest pain, or dyspnea) was there a statistically significant advantage to regadenoson over adenosine. However, it was not said why these 3 symptoms were selected out, and other symptoms such as headache, nausea, angina pectoris, or chest discomfort were not included. This violates basic statistical principles and could be though of as data mining. It is important to not that the research to date has been heavily supported by the manufacturer of regadenoson, with several authors having financial ties to the company. This may explain in part why a new “tolerability score” was developed, and selective symptom scores created. When only looking at severe events, to date, regadenoson has not been shown to be superior to adenosine. No direct comparisons have been made between regadenoson and dipyridamole in terms of a “Tolerability Score” or side-effect profile. We can confidently say that neither adenosine nor regadenoson have been clearly shown to be superior to dipyridamole in terms of patient safety, patient tolerability, or clinical utility. The latest Stress Protocols Guidelines from the American Society of Nuclear Cardiology states that the frequency of minor side effects is less with dipyridamole as compared to adenosine. Furthermore, the incidence of AV block with dipyridamole is less than that observed with adenosine. However, no large studies are available to compare the rates of major side effects of these three agents.

What we do know is the dipyridamole is as safe as exercise stress testing. The largest study of dipyridamole was a multinational study looking at 73,806 patients (Lette et al J Nucl Cardiol. 1995 Jan-Feb;2(1):3-17). In this group of patients undergoing hospital-based dipyridamole cardiac stress myocardial perfusion imaging, there were 7 cardiac deaths, 13 nonfatal myocardial infarctions, sustained ventricular arrhythmias in 6 patients requiring cardioversion, and 9 cases of acute bronchospasm. For exercise treadmill testing, the rate of severe complications is about 5 in 10,000 with 1 of these being cardiac death and the other 4 non-fatal myocardial infarction. This is almost identical to the dipyridamole rate of 0.95 cardiac deaths per 10,000 and 3.8 non-fatal but serious side-effects per 10,000. The rate of side-effects in an outpatient population is known to be significantly less.

It remains possible that regadenoson will ultimately be shown to have a lower rate of serious side effects compared to dipyridamole. However, it is also possible that the rate of side effects is higher than dipyridamole. This is a distinct possibility, given that it has been shown that adenosine has a higher rate of side effects compared to dipyridamole. What is clear is that dipyridamole is significantly less expensive than either adenosine or regadenoson, and the regadenoson research has been heavily supported by industry, which has both sponsored the research and hired several of the authors to be consultants or participate in their speakers’ bureau.

**Conclusion(s)**

It is my opinion that regadenoson may be a preferred cardiac stress agent, but in selected patients only. Subjectively, it has been shown to make people feel better compared to adenosine (the “Tolerability Score”). This feeling likely results from real, physiologic processes. However, is this short-term benefit worth the difference in price? These nonspecific symptoms are almost always rapidly reversed with aminophylline. Many physicians, including myself, routinely administer aminophylline at the end of an outpatient dipyridamole stress test in an attempt to limit or prevent the development of these symptoms.

There also may be an important benefit from being able to give regadenoson over 10 seconds, compared to the 4 minute infusion time required for dipyridamole. This time difference may mitigate the difference in price between the two agents.

It is important to practice evidence-based medicine
when looking at regadenoson compared to dipyridamole, and not hastily rush to a conclusion prior to the data coming out. I still remember in the late 1990's the rush to put post-menopausal women on hormone replacement therapy. This turned out to be a problem, and we've since learned an important lesson. Hormone replacement therapy isn't right for every post-menopausal woman, and can cause significant harm. Similarly, I am concerned that the argument for regadenoson relies almost exclusively upon theory and business marketing, and not enough upon the scientific evidence.
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