Safer stress tests for myocardial perfusion imaging

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In this issue of the *Journal of Nuclear Cardiology*, Andrikopolou et al.[1] conducted a systematic review of the safety of vasodilatory stress tests using adenosine and regadenoson for myocardial perfusion imaging (MPI). By searching SCOPUS with the predefined keywords, they selected 34 studies which include 22,957 patients. Among 34 studies, adenosine was used in 21 and regadenoson in 15, while both were used in two studies. The estimated incidence of overall and high-grade atrioventricular block (AVB) was 3.81% (95% CI 1.99%-6.19%) and 1.93% (95% CI 0.77%-3.59%), respectively. The incidence of AVB and high-grade AVB in adenosine group was 8.58% (95% CI 5.55%-12.21%) and 5.21% (95% CI 2.81%-8.30%), while that in regadenoson group was 0.30% (95% CI 0.04%-0.82%) and 0.05% (95% CI < 0.001%-0.19%), respectively. They concluded that both overall and high-grade AVB are significantly less frequent with regadenoson compared to adenosine.

Adenosine is a naturally occurring ligand of four distinct subtypes (A1, A2A, A2B, and A3) of cell membrane G protein-coupled receptors. It produces coronary artery vasodilatation by activating adenylyl cyclase that results in the opening of potassium channels. The opening of these channels in vascular smooth muscle cells hyperpolarizes the cells and inhibits voltage-gated calcium channels and intracellular calcium release, resulting in relaxation.[2] The common actions of adenosine on different types of adenosine receptors are associated with several life-threatening side effects. Actions on the A1 receptor can induce AVB, while actions on A2B and A3 receptors can induce bronchoconstriction especially in patients with asthma or severe chronic obstructive pulmonary disease (COPD). The use of adenosine can be limited in a substantial number of patients as the prevalence of COPD can be found in 30% patients undergoing adenosine MPI.[3]

Regadenoson, an A2A selective agonist, is used as a pharmacologic stress vasodilator for MPI. It was approved by the US Food and Drug Administration (FDA) on April 10th, 2008, and on September 6th, 2010 by the European Medicine Agency. It has comparable accuracy and non-inferiority to adenosine in regard to detection of perfusion defects by nuclear perfusion imaging. Regadenoson has been used successfully in patients with chronic kidney disease (CKD), COPD, asthma, and liver disease and needed MPI.[4] Remarkably low incidence of bronchoconstriction by regadenoson was reported,[5] which can be explained by the fact that regadenoson selectively binds with the A2A receptors only and does not with the A3 receptors, which induce mast cell activation and smooth muscle constriction of the airways.

There are some concerns about the diagnostic efficacy of regadenoson. Gould et al.[6] first described the importance of inducing hyperemia for the diagnosis of coronary artery disease. The vasodilatory reserve is exhausted in stenosed arteries to preserve a baseline perfusion as a compensatory mechanism. The contrast between normal and stenosed arteries can be maximized by the induction of hyperemia

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during MPI as the increase in myocardial perfusion in response to vasodilatory stimulation is diminished in atherosclerotic coronary lesions. A recent study by Johnson and Gould[7] showed only around 80% of vasodilatory efficacy by regadenoson stress, with reference to dipyridamole stress. Even by changing the radiotracer injection time from 10 to 20 seconds to 55 seconds after the regadenoson bolus, the absolute stress flow increase was limited to around 90% of that induced by dipyridamole stress. Because the assessment of the functional severity of coronary artery disease mainly depends on the perfusion during stress, insufficient vasodilatory efficacy may lead to decreased diagnostic performance of MPI. Despite the lower vasodilatory efficacy, competent diagnostic accuracy of regadenoson stress imaging for coronary artery disease was shown in MPI,[8] stress cardiac CT perfusion,[9] and stress echocardiography[10] studies. The tradeoff between the diagnostic efficacy and safety of the MPI study using regadenoson has not been fully clarified, but seems to be clinically acceptable.

Exercise stress is regarded as the best physiologic approach for the purpose of achieving hyperemia. The limitation of the exercise test is that it is not applicable to patients with an abnormal baseline electrocardiography (ECG), or those who are to undergo positron emission tomography (PET) study with radiotracers of short half-lives. Pharmacologic stress agents have been used for these groups of more complicated cases. Adenosine is widely accepted as a readily accessible pharmacologic substitute for the exercise stress tests. As adenosine is a non-specific adenosine receptor agonist, it is associated with life-threatening side effects.

Several different approaches have been suggested to reduce the side effects of pharmacologic stress tests (Table 1). The first approach is a new vasodilatory agent for hyperemic stimulation. Nicorandil, a coronary macrovascular and microvascular dilating agent, has recently been validated in terms of its efficacy and safety.[11] The vasodilatory effects of nicorandil involve the increase in production of cyclic guanylate monophosphate as a donor of nitric oxide and activation of adenosine triphosphate-sensitive potassium channels. It also inhibits the occurrence of major adverse cardiac events after coronary revascularization especially in CKD patients and improves the recovery of myocardial fatty acid metabolism.[12] Nicorandil is mainly used for invasive studies such as the measurement of fractional flow reserve (FFR). It is administered via intra-coronary (IC) route. A routine protocol includes a bolus injection of nicorandil 2 mg via IC route, as it is known to provide an equivalent vasodilatory efficacy to 140 ug/kg/min of intravenous (IV) adenosine. If nicorandil is to be injected via IV, a much higher dose is required, but its vasodilatory efficacy has not been clarified yet.

Another approach is to avoid hyperemic stimulation per se. Instantaneous wave-free ratio (iFR) is arising as a novel parameter without the need for the induction of hyperemia. This issue is now being settled through clinical practice by showing its competent diagnostic accuracy[13] and a non-inferior prognostic value[14] in comparison with FFR. Unfortunately, these approaches are not easily applicable to MPI. The wave-free period is only a part of the diastole which should be defined by an invasive measurement of coronary pressure. The general ECG gating using 8 or 16 bins per cardiac cycle does not usually allow for the specification of this period for MBF measurement without stress. Moreover, it is not possible to distinguish the accumulated radioactivity according to specific cardiac contraction phases.

Dobutamine is an inotropic stress agent and is also commonly used instead of adenosine in patients with asthma or COPD. But its hyperemic efficacy neither fully matches the clinical need, nor is it sufficiently safe.[15] More A2A-receptor-specific agents, including binodenoson, regadenoson, and apadenoson, were introduced to overcome the adenosine-associated risks in the field of pharmacologic stress MPI.[16]

By adding exercise, the duration of adenosine or dipyridamole infusion could be shortened, which might result in fewer side effects during stress testing in patients undergoing MPI.[17,18] Moreover, by combining pharmacologic stress with low-dose exercise, splanchnic blood can be redistributed to the skeletal muscles, resulting in decreased liver or bowel activity and therefore better image quality.[19] The levels of adjunctive treadmill exercise usually depend on the patient's physical ability to exercise and achieve targeted heart rate. Regadenoson is also being investigated for its possible combination with variable timing and degrees of exercise. The safety and tolerability of this approach have been repeatedly demonstrated. Kwon et al.[20] found that a regadenoson exercise protocol, which combined regadenoson injections with low-level treadmill exercise was safe and well tolerated without severe hemodynamic side effects in 1263 patients, even those with a high prevalence of COPD/asthma (16%). Several studies consistently showed less side effects from regadenoson with an adjunctive exercise protocol even in comparison with regadenoson-only.[21–25] To optimize the use of regadenoson plus exercise protocols, regadenoson can be adjunctively administered for selected patients who could not achieve a maximal predicted heart rate during exercise. In terms of diagnostic feasibility, the most recent prospective study, the EXERRT trial[24] found non-inferior diagnostic agreements of regadenoson at an early recovery phase from submaximal exercise as compared to regadenoson stress only at 1 hour after full recovery from submaximal exercise.

Table 1. Approaches to reduce side effects induced by pharmacologic stress

Approaches	Examples
MPI	
New pharmacologic agents	A2A-receptor-specific agents (binodenoson, regadenoson, apadenoson)[16]
Addition of exercise stress	4-min adenosine + submaximal exercise[17]
	4-min dipyridamole + maximal exercise[19]
New agent + exercise[a]	Regadenoson + low-level exercise[20,21]
	Regadenoson at peak exercise[22]
	Regadenoson + peak or low-level exercise[23]
	Adjunctive regadenoson for submaximal exercise[24]
Invasive measures	
New pharmacologic agent	IC nicorandil[11]
Omitting vasodilatory stress	iFR[13,14]

MPI, myocardial perfusion imaging; *IC*, intra-coronary; *iFR*, instantaneous wave-free ratio
[a]Adjunctive exercise protocols were grouped following the classification by Mahmarian[25]

In summary, among many pharmacologic stress test agents, regadenoson can be regarded as an ideal agent in terms of safety and simplicity. It is much safer than adenosine both in terms of AVB and bronchoconstriction. Its injection method (400 μg bolus IV) is much simpler, as compared to administering a continuous infusion of adenosine and dipyridamole. Although the hemodynamic efficacy for optimal assessment of stress myocardial perfusion seems somewhat suboptimal, recent studies in various imaging modalities encourage the use of regadenoson as a competent stress agent in the diagnosis of coronary artery disease.

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