Advanced hybrid stress testing: A potential new paradigm combining exercise and pharmacologic stress

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Partington et al¹ at the Brigham & Women's Hospital present a landmark article on the use of pharmacological stress at near peak exercise in this issue of the *Journal*. The article represents the first in a likely series of articles by these and other investigators exploring the use of selective A2 agents injected as a bolus at near-peak exercise, or during recovery, in patients undergoing maximal exercise testing with myocardial perfusion imaging (MPI) who do not achieve the accepted 85% maximum heart rate standard.

“Hybrid stress testing,” the combination of exercise and vasodilation pharmacologic stress with dipyridamole, adenosine, or regadenoson, improves patient tolerance and image quality compared to pharmacologic stress without exercise.^{2–8} While off label, supplemental exercise during dipyridamole and adenosine stress is recommended by ASNC.⁹

As almost all patients can undergo either exercise or pharmacologic stress, the development of pharmacologic stress has allowed MPI to become the most commonly performed test in the US for the evaluation of ischemia. Pharmacologic stress testing continues to increase in the US, representing 51% of MPI studies in 2010 and 55% in 2011.¹⁰ A substantial percentage, though the minority, of these studies are performed in a

hybrid fashion with low level exercise combined with pharmacological stress.

Partington and colleagues seized upon the specific advantages of regadenoson (bolus administration over 10 seconds and one dose for all patients) to evaluate maximal vasodilation stress with regadenoson injected at near-peak exercise in 211 relatively low-risk patients who could not achieve >85% of maximum heart rate (220 – age). Beginning with 2,237 patients undergoing MPI and able to exercise in their observational trial, 1,522 (68%) achieved >85% of maximum heart rate and, therefore, did not require regadenoson. The remaining 715 patients received either (a) radiotracer despite a heart rate ≤85% maximum (ETT-Submax, n = 504, 23%) or (b) a novel protocol of regadenoson injected 1 minute prior to exercise termination, with radiotracer (Tc-99 sestamibi) injected 30 seconds following regadenoson (n = 211, 9%). They labeled this new test “ETT-Reg.” Patients who underwent regadenoson stress MPI while supine (Supine-Reg, n = 239) during the same time period served as another comparison group.

Patients who had ischemic ECG changes or symptoms of ischemia during exercise stress received radiotracer when this occurred so were part of the ETT-Submax group.

Patients were excluded from the ETT-Reg group a priori if, prior to the initiation of stress testing, they had (a) undergone past coronary revascularization, (b) a Q wave myocardial infarction on their resting ECG, (c) known CAD and were being evaluated for ischemia at the workload achieved, even if exercise was submaximal, (d) CAD and were undergoing MPI for symptoms suggestive of ischemia.

The decision to exclude patients from ETT-Reg during the test included the clinician's belief that adding regadenoson to maximal exercise, albeit submaximal by heart rate, was unsafe in a particular patient based on signs or symptoms exhibited during exercise.

Such exclusions resulted in the ETT-Reg group patients comprising a low-risk group compared to the comparison groups. Acknowledging this, the investigators found ETT-Reg to be feasible, safe, and significantly better tolerated than regadenoson administered

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Figure 1. Potential stress testing algorithm integrating advanced hybrid imaging if further studies demonstrate the safety of ETT-Reg or Ex2Reg (see text). Contraindications refer to the relative contraindications in Table 1 of societal guidelines.¹⁵ Clinical judgment refers to that of the ordering or testing clinician. *RV*, Right ventricular; *max*, maximum; *HR*, heart rate.

supine. Vasodilator-related adverse events: flushing, dizziness, light-headedness, and gastrointestinal symptoms, occurred in 49% of patients in the ETT-Reg group compared to 6% in the Supine-Reg group. Similarly, aminophylline was required in 8.1% of Supine-Reg patients compared to only 0.5% of the ETT-Reg patients.

Initiating regadenoson selectively by allowing patients to attempt maximal exercise has important implications. Cost could lessen with fewer patients requiring pharmacologic stress, prognosis could potentially be better evaluated using exercise duration and exercise-induced symptoms could be evaluated.¹¹ What are the potential downsides of a stress testing strategy that includes an ETT-Reg option?

In a preliminary report, Thompson et al¹² found excessive hypertension or hypotension to occur not infrequently in their early report of the use of regadenoson given at near-peak, but submaximal exercise. Excessive hypertension or hypotension was infrequently observed by Partington and colleagues. This may have been secondary to methodological differences; however, as blood measure was measured several times within first 2 minutes of regadenoson administration in Thompson's report while measured at the 2-minute mark post-regadenoson in Partingtons.

In the resting state, the response of systolic blood pressure to regadenoson is variable, increasing in some

and decreasing in others.¹³ While the hypotensive response is likely related to vascular A2a receptor activation, the hypertensive response is likely elicited by stimulation of the A2A receptors in the carotid body. Stimulation of these latter receptors results not in vasodilation but in norepinephrine release.¹⁴ Dhalla et al¹⁵ demonstrated a doubling of plasma norepinephrine levels in the rat model by 2 minutes following regadenoson administration. Further evaluation of blood pressure response with regadenoson at near-peak exercise is warranted.

Another challenge with ETT-Reg is the co-morbidities of patients undergoing exercise testing. Individuals in whom exercise MPI testing is performed with some trepidation are likely poor candidates for the "double stress" of ETT-Reg. Table 1 of the 2002 societal guidelines lists those with relative contraindications to exercise.¹⁶ Excluded patients with these contraindications would be prudent at this early juncture in the evaluation of ETT-Reg. Such contraindications include moderate to severe asymptomatic aortic stenosis, hypertrophic cardiomyopathy, very recent myocardial infarction and symptoms likely representing unstable angina.

The use of nontraditional electrocardiographic changes to evaluate for ischemia and potential injection of radiotracer should not be ignored. Increasing p-wave duration¹⁷ and ST elevation in AVR¹⁸ have significant

potential as measures of ischemia and merit further evaluation.

An alternative approach using regadenoson at near-peak exercise in patients not achieving 85% maximum predicted heart rate is continuing exercise to the maximum tolerated and injecting regadenoson during a walking recovery period (Ex2Reg). This approach is logistically easier than injecting regadenoson and radiotracer prior to exercise test completion. More importantly, it provides the opportunity to evaluate the ECG during recovery. Rywik et al¹⁹ evaluated 216 asymptomatic patients who developed ischemic ECG changes during exercise testing and found that changes occurred only during recovery in 27%. Injecting regadenoson at near-peak exercise with ETT-Reg creates a potential hazard if substantial ischemic ECG changes were to develop in recovery resulting in a clinician regretting the “double stress” created with the injection of regadenoson to a patient who was likely already ischemic at near-peak exercise.

The use of regadenoson during recovery may also be friendlier from a hemodynamic standpoint. Excessive hypertension or hypotension would be expected to occur less frequently if regadenoson were injected during low level recovery exercise compared to maximum exercise.

A large randomized clinical trial of regadenoson injected during a walking recovery period is now underway.²⁰ If further studies demonstrate the safety of regadenoson at near-peak exercise or during recovery, hybrid testing could be more deeply integrated into an overall stress testing strategy. Such a potential algorithm is represented in Figure 1. This strategy could minimize the use of pharmacologic stress as many patients referred for pharmacologic stress would likely achieve $\geq 85\%$ maximum heart rate if given the opportunity. Decreasing the need for a separate pharmacologic stress study following an inadequate stress study could improve lab efficiency and the patient experience. A rigorous evaluation of the safety and feasibility of this strategy is welcomed.

Partington and colleagues and other investigators of this novel protocol have initiated the potential of a new paradigm in stress testing.

Conflict of interest

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