Combined pharmacologic and low-level exercise stress protocols for radionuclide myocardial perfusion imaging

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INTRODUCTION

The use of pharmacologic vasodilator stress agents is indicated for radionuclide myocardial perfusion imaging (MPI) in patients unable to exercise to an adequate workload (at least 85% of age-adjusted maximal predicted heart rate [HR] and five metabolic equivalents unless overt ischemia occurs before these thresholds). Compared to exercise, the most physiological stimulus, dipyridamole and adenosine have several limitations, including low sensitivity of the stress electrocardiogram (ECG) for ischemia and frequent side effects. Further, both agents induce dilatation of the splanchnic vasculature resulting in a higher concentration of radiopharmaceuticals in the liver and intestinal tract, which could interfere with image intrepretation.[1]

In response to these limitations, protocols combining dipyridamole or adenosine with exercise have been established in the past several years.[2-4] Adding exercise to vasodilator stress promotes a redistribution of blood flow to the skeletal musculature and away from intra-abdominal organs such as the liver.[5] These effects result in a higher heart-to-liver activity ratio and better image quality compared to vasodilator infusion alone.[2,6-9] The addition of low workload exercise to vasodilator stress also reduces side effects compared to vasodilator infusion alone.[10-13] Lastly, images can be acquired earlier, after administration of the radiopharmaceutical in patients undergoing a combined exercise/vasodilator protocol compared to vasodilator alone, with potential for detecting myocardial stunning.[2,14] It should be acknowledged, however, that many patients, particularly inpatients, are physically unable to perform exercise during pharmacologic stress.

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PATIENT SELECTION

The combined protocol should be considered in the following conditions (Table 1).

1. Patients with a tendency to bradycardia and/or hypotension. Adding exercise to vasodilator stress decreases the risk of worsening bradyarrhythmias and hypotension. Therefore, those with resting bradycardia or known conduction disease (with the exception of left bundle branch block or patients with right ventricular pacemakers) should be considered for the combined protocols as should those with low baseline blood pressures, particularly when adenosine stress is to be employed.[7-9,13,15,16]
2. Patients with past difficulties with vasodilator MPI and/or non-diagnostic MPI studies (including some with exercise stress studies) are good candidates for the combined protocols. For example, in those with imaging artifacts, the addition of exercise may decrease gastrointestinal and hepatobiliary uptake of tracer resulting in improved image quality.[7,8,17,18]
3. Patients who are unable to achieve target HR either due to physical deconditioning, chronotropic incompetence, or an inability to safely discontinue medications likely to blunt the HR response to exercise (e.g. beta blockers and non-dihydropyridine calcium channel blockers).
4. Patients who have had significant side effects during a previous vasodilator studies. Because of likely improved patient tolerability, those who have had significant side effects during past vasodilator studies should be considered for these protocols as well.[7-10,12,13,16] Using a combined protocol may also improve patient satisfaction by allowing for a shorter study time due to the ability to image sooner after stress injection.[7]
5. Patients who are not expected to reach target HR but in whom some assessment of exercise capacity is desired (e.g. those with exertional symptoms).
6. Patients who are not expected to reach target HR, but in whom an assessment for exercise-induced arrhythmias is desired.

Table 1. Patients who may benefit from combined pharmacologic/exercise stress protocols

Not expected to reach target heart rate but information regarding exercise capacity, hemodynamic response to exercise, and arrhythmias would be useful.
Unable to discontinue medications known to blunt the heart rate response to exercise (e.g. beta blockers and certain calcium channel blockers)
Those with bradycardia and/or conduction blocks
Those with marginal blood pressures at rest or at risk for hypotension
Those with past or anticipated adverse side effects from pharmacologic stress agents
Those with past or anticipated problems with image quality due to gastrointestinal or hepatobiliary uptake of tracer
Those with exertional symptoms not expected to reach target heart rate

While practitioners may want to consider adding exercise to pharmacologic stress in all of their able patients referred for vasodilator myocardial perfusion imaging, there are certain subgroups where the combination is best avoided. These include patients with left bundle branch block and right ventricular pacing. The increased heart rates seen with exercise stress have been associated with the presence of perfusion defects in the absence of angiographic coronary artery disease, and decreased diagnostic accuracy in these patients.[19-21] As well, some patients physically are not able to perform exercise and are not candidates for combined protocols.

PROTOCOLS

Patient Preparation for Combined Vasodilator and Exercise Stress

Theophylline and other xanthines should be withheld for at least 72 hours and all caffeine and caffeinated beverages/foods for at least 12 hours prior to vasodilator infusion.[22] Special attention should be focused on complete discontinuation of coffee, tea, chocolate, and soft drinks. Patients taking oral dipyridamole (as antiplatelet therapy) should stop it for 48 hours prior to vasodilator infusion. Since caffeine is cleared by the liver, longer avoidance of compounds containing it should be considered in patients with hepatic failure, especially those being evaluated prior to liver transplantation.[23]

Adenosine with Exercise

In North America, treadmill exercise is usually added to the adenosine infusion in combined exercise/adenosine protocols. However, the first reports of combined protocols were from Europe and bicycle exercise was utilized.[9,24] When planning to perform exercise stress along with the adenosine infusion, one must consider the duration of the infusion and exercise, the timing of the tracer injection, and the type and intensity of exercise.

An early publication in this area by Elliott and colleagues utilized a 4-minute adenosine infusion with 6 minutes of exercise.[8] As this was one of the earliest studies combining adenosine and treadmill exercise, the investigators had the patients walk for 1 minute before starting the adenosine infusion to make sure the patients could walk adequately before continuing the protocol. Exercise was continued for a minute after the infusion was stopped to make the test length comparable to the standard 6-minute infusion. Most studies have started the adenosine infusion and exercise at the same time.[7,13,17,25] The duration of the adenosine infusion has varied from 4 to 6 minutes in these reports. One multicenter trial found no difference in the sensitivity for detection of coronary disease (confirmed by invasive coronary angiography) between the 4-minute adenosine protocol and the 6-minute standard protocol without exercise.[26]

In general, exercise has been performed simultaneously for the duration of the infusion and the tracer has been injected half-way through the adenosine infusion, whether the infusion duration was 4 or 6 minutes.[7,8,17] In one study, the infusion was 5 minutes long and the tracer was injected 2 minutes into the infusion.[13] These protocols all conform to the ASNC Clinical Update on adenosine stress protocols[27] allowing time for maximal vasodilation and adequate circulation of the tracer after injection. There are no data suggesting that adjunctive exercise changes the pharmacokinetics of adenosine allowing for a shorter infusion or change in the timing of tracer administration.

Another consideration in protocol design is the level of exercise. In the literature this has ranged from 1.0 mph at 0% grade (and decreased if needed)[7] to a full symptom-limited Bruce protocol.[25] Most reports and most laboratories appear to use stage 0 of a modified Bruce protocol (1.7 mph, 0 grade) with adjustments made as necessary to account for each patient's ability.[7]

Adenosine with concomitant exercise has been shown to be safe and better tolerated by patients. Studies have demonstrated a reduction in side effects.[7-9]

Dipyridamole with Exercise

Most patients for the combined protocol are exercised at low workload as per the patient's abilities, which can be limited to the earlier stages of the Bruce protocol, or some low workload alternative such as the modified Bruce, Kattus, or Naughton protocols. The workload can be increased as the patient's ability allows, but if nearing a limit, then exercise should be maintained at a lower level (limited to stage 1 or 2 of the protocols described) rather than pursuing a higher stage. With exercise plus dipyridamole, the maximum action of the drug occurs between 6 and 9 minutes into the infusion; therefore the infusion may start along with or even before exercise begins.[14] The radiotracer is injected 3-5 minutes after the completion of dipyridamole infusion.

CONCLUSION

When possible, low-level exercise performed in combination with pharmacologic stress perfusion imaging results in less side effects and better image quality than vasodilator stress alone. Further, this combination provides an objective assessment of functional capacity and the heart rate response to exercise. The protocols recommended can be readily implemented in a nuclear cardiology laboratory. However, since increasing the heart rate of patients with LBBB can result in artifactual findings on myocardial perfusion imaging, low-level exercise supplementation is best avoided in these patients and in patients that are unable to tolerate modest levels of exertion.

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