Provisional use of myocardial perfusion imaging in patients undergoing exercise stress testing: A worthy concept fraught with challenges

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It has been recognized for many years that patients who achieve a high workload on exercise stress testing have an excellent prognosis, particularly in the absence of ischemic ST segment depression.^{1–4} Outpatients with a low-risk Duke Treadmill Score (based on exercise duration, magnitude of ST deflection and an angina index) had an observed annual mortality rate of only 0.25%.⁵ Exercise capacity has been shown to be a better predictor of all-cause mortality than maximum exercise heart rate.¹ Myers et al¹ reported that patients achieving a workload of ≥ 10 metabolic equivalents (METs), even in the presence of cardiovascular disease, had a relatively low risk of death during follow-up. For every 1-MET increment in peak treadmill workload, there was an associated 12% improvement in survival. These investigators found that, in both healthy subjects and those with cardiovascular disease, the peak exercise capacity was a stronger predictor of an increased risk of death than clinical variables or coronary artery disease (CAD) risk factors such as hypertension, smoking, and diabetes. It had greater prognostic value than peak exercise heart rate, ST depression, or exercise-induced arrhythmias. Morise et al⁶ found a 14% reduction in cardiac events among subjects < 65 years of age, and an 18% reduction among subjects ≥ 65 years of age for

each 1-MET increase in workload. After adjustment for age, the peak METs achieved was the strongest predictor of subsequent mortality. In another study, among patients with a positive exercise ECG, who achieved ≥ 10 METs, 93% had a negative exercise echocardiogram and less than 1% mortality after 7.2 years of follow-up.⁷

More recently, Bourque et al⁸ from the University of Virginia reported that in more than 470 consecutive patients referred for exercise SPECT myocardial perfusion imaging (MPI), who achieved $\geq 85\%$ of maximum predicted heart rate (MPHR) and ≥ 10 METs, the prevalence of significant ischemia defined as comprising 10% or more of the left ventricle (LV), was only 0.4%. In fact, no patient who achieved ≥ 10 METs without ischemic ST depression had significant ischemia on MPI. The prevalence of 5–9% LV ischemia in such patients was also very low at 0.7%. This population had an intermediate-to-high pretest likelihood of CAD, with 20% having known CAD and 70% with chest pain as the indication for testing. Ischemia involving $\geq 10\%$ of the LV was also low (2.4%) in the 82 patients who achieved ≥ 10 METs, but $< 85\%$ of MPHR. Bourque et al⁹ then published the subsequent cardiac mortality and nonfatal cardiac event rates in this patient cohort achieving ≥ 10 METs. They reported a remarkably low annual cardiac mortality of 0.1% and a combined annual cardiac death or nonfatal myocardial infarction rate of 0.4%. None of the event patients had either $> 5\%$ or $> 10\%$ LV ischemia, and none was in the subsets which achieved $< 85\%$ of MPHR or who had ST depression. Therefore, even if perfusion imaging was performed, it would not have identified the patients who subsequently had events. Interestingly, the annual cardiac death or nonfatal infarction rate was lower in patients who achieved ≥ 10 METs than observed in patients with normal stress perfusion scans regardless of workload achieved. These studies by Bourque et al,^{8,9} together with prior published reports relating the excellent prognosis in patients achieving high exercise workloads, bring into question the added prognostic value, and cost-effectiveness of MPI or stress echo in patients achieving ≥ 10 METs and no ischemic ST depression, regardless of the exercise heart rate and whether they have a history of prior CAD.

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In this issue of the journal, Duvall et al,¹⁰ recognizing that the results of MPI seemed to add little to risk assessment of patients who exercise to 10 METs or more during stress testing, seek to determine if a provisional tracer injection protocol could be developed in which a patient would not have the tracer administered intravenously if ≥ 10 METs was achieved without symptoms and with a negative stress ECG response. They retrospectively reviewed all patients who underwent a SPECT MPI study over a 6.5-year period and estimated how many patients might have been eligible for a “standby injection” protocol with provisional MPI. The criteria they employed for identifying this noninjection group included no known CAD, <65 years of age, an interpretable rest ECG, attaining $\geq 85\%$ of MPH, achieving ≥ 10 METs with no symptoms of chest pain or significant dyspnea, and manifesting no ischemic ST depression or exercise-induced arrhythmias. They determined that 6.3% of their total cohort of approximately 25,000 patients who underwent SPECT MPI during this survey period fulfilled these criteria and would not have been injected with a tracer for MPI. Abnormal perfusion on MPI was seen in 5.9% of the hypothetical noninjection group, with only 1.3% having a stress perfusion defect of $>10\%$. At approximately 5 years of follow-up, all cause mortality was just 1.1% in those patients who would not have been injected with tracer. Interestingly, of the approximate 5,300 patients in this cohort eligible for the provisional imaging protocol before testing because they were referred for exercise testing, were <65 years of age with no known CAD, and had an interpretable baseline ECG, only 29% would not have been injected because of failure to fulfill all criteria described above.

The number of patients who might not have been injected with tracer for MPI could have been expanded if Duvall et al¹⁰ did not include shortness of breath as an endpoint or included patients with an intermediate pretest likelihood of CAD who were >65 years of age. Patients were withdrawn from the provisional imaging protocol if they had right bundle branch block on their resting ECG. Such patients do have interpretable ST segment changes during testing. Also, dyspnea in patients achieving high workloads with no ST depression should not necessarily eliminate them from eligibility for a noninjection protocol. Bourque et al⁹ found an excellent prognosis in patients achieving ≥ 10 METs but less than 85% of MPH. Such patients who do not exhibit ST depression or limiting angina might also be eligible for a noninjection protocol. Outcome data regarding patients who were >65 years of age, had dyspnea as an endpoint, or had ≥ 10 METs but $<85\%$ of MPH are not provided. Further clinical research appears warranted to determine if such patients also

have a low prevalence of ischemia by MPI and a good prognosis. This would expand the pool of patients referred for exercise stress testing for which MPI might not add additional prognostic information to achieving ≥ 10 METs without ST depression.

There are several challenges that would be faced by nuclear cardiology laboratories in implementing such a provisional use of MPI with exercise testing. First, referral physicians and payers would have to agree beforehand that a noninjection protocol would be applied to their patients if they were eligible based on whatever predetermined criteria that were established. Second, insurance companies and Medicare would have to create a new code to cover the cost of an IV, supplies, and unused radioisotope, balanced against the reduced technical and professional charges for the stress test vs an MPI. Third, patients themselves would need to be reassured that not performing MPI would result in an adequate diagnosis of their symptoms and valid risk assessment. A fourth issue is who would decide if tracer should be administered, as in many practice settings, a registered nurse or an exercise physiologist performs the stress test with a physician supervising but not actually present. These are logistics that need to be worked out.

Some referring physicians may not agree with stress-testing personnel, not familiar with the patient's specific circumstances, deciding on the optimal study. Each patient is unique, and the studies referenced above refer to population and not patient-specific outcomes. In daily practice, one sometimes encounters patients with very concerning but not frequently occurring symptoms. One example is a patient who jogged several times a week, usually without symptoms, but who requested assessment because sometimes during jogging, he became suddenly dyspneic and light-headed and felt a sense of doom. During his MPI, he achieved 10.1 METs without chest pain or ST changes, but the images revealed a large area of hypoperfusion anteriorly and apically (see figure, courtesy of Dr Iain McGhie of Saint-Lukes Cardiovascular Consultants). Coronary angiography showed a high-grade proximal LAD stenosis. His coronary artery calcium score was 3.

Given the logistic, economic, billing, and potentially legal (can a lab substitute an ordered test for another without specific authorization from the referring physician?) issues associated with a provisional imaging strategy, perhaps providers should also consider whether the pendulum has swung too far in favor of stress imaging as an initial test. For example, most patients with normal resting ECGs who might have the capability to achieve ≥ 10 METs might best be triaged initially to nonimaging exercise stress testing. The Duke Activity Status Index (DASI) is a simple self-administered 12-item questionnaire that predicts METs likely to

be achieved on exercise treadmill testing.¹¹ Being able to predict beforehand which patients are most likely to achieve high workloads would reduce the number of radioisotope doses prepared for provisional imaging. The “What Is the Optimal Method for Ischemia Evaluation in Women?” (WOMEN) trial used the DASI to identify women with suspected CAD, an interpretable ECG, and ≥ 5 METs who were randomized to standard initial exercise ECG testing or to exercise MPI.¹² At 2 years, there was no difference in major adverse cardiac events between the two groups. A strategy of initial exercise ECG testing yielded similar outcomes vs exercise MPI while providing significant diagnostic cost savings. Thus, this is one example where a pretest evaluation of functional capacity was used to identify a low-risk subgroup of exercising women who do not appear to benefit from initial as opposed to adjunctive

MPI. Their survival free score of CAD death or hospitalization for an acute coronary syndrome or heart failure was 98.8% at 2 years. Another option is stress-first/stress-only imaging if the stress image is normal.^{13,14} Optimally, given the low-risk of the population under consideration, this would be performed using one of the newer cameras that permit very low tracer dosages.

One approach for patient and referral physician reassurance that elimination of MPI would not miss patients with significant CAD, is to have patients who achieve ≥ 10 METs with no ST depression, and not injected with tracer, but are still at intermediate risk based for CAD based on the type of chest pain experienced and having multiple risk factors for CAD including diabetes, undergo CT coronary calcium imaging (CAC).¹⁵ Those exhibiting limiting dyspnea as

an exercise endpoint, and perhaps those aged 65-70 years might also benefit from CT CAC if they achieve a high workload with no ST depression. This would permit the detection of coronary atherosclerosis and lead to more aggressive medical therapy than might otherwise be undertaken after the negative ECG stress test. In addition, for patients with high CAC scores (e.g., >300), a repeat stress test with MPI could be performed for further refining risk. Note, however, that in the patient example described above, the CT CAC score was only 3. In the challenge of test selection, there must always be weight placed on clinical acumen. This is perhaps the greatest drawback of a protocol having laboratory personnel making a decision of substituting one test for another without intimate knowledge of a patient's unique circumstances.

It should be pointed out that the most current update of the stable angina guidelines¹⁶ indicate that standard exercise ECG testing is recommended for patients with an intermediate pretest probability of ischemic heart disease, who have an interpretable ECG and at least moderate physical functioning, or no disabling comorbidity. This is a Class I recommendation. It is further stated (as a Class IIa recommendation) that exercise MPI is "reasonable" for patients with an intermediate-to-high pretest probability of obstructive ischemic heart disease who have an interpretable ECG and at least moderate physical conditioning. Based on the data regarding the very low prevalence of significant ischemia and excellent prognosis for patients achieving ≥ 10 METs without ischemic ST depression, the provisional injection protocol, with perhaps some expansion of criteria for eligibility, warrants further consideration and prospective evaluation. This approach might best identify which patients do not require MPI at the outset for evaluation of symptoms suggestive of CAD. The addition of CT CAC imaging in the clinically higher risk patients with negative exercise ECG stress tests at high workloads also warrants a prospective clinical trial to determine its value. Certainly, a nonimaging exercise ECG stress test could be performed alone as the first test in patients prospectively identified as having good functional capacity and deemed at low or low-intermediate pre-test probability for CAD.

References

1. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med* 2002;346:793-801.
2. Snader CE, Marwick TH, Pashkow FJ, Harvey SA, Thomas JD, Lauer MS. Importance of estimated functional capacity as a predictor of all-cause mortality among patients referred for exercise thallium single-photon emission computed tomography: Report of 3,400 patients from a single center. *J Am Coll Cardiol* 1997;30:641-8.
3. Goraya TY, Jacobsen SJ, Pellikka PA, et al. Prognostic value of treadmill exercise testing in elderly persons. *Ann Intern Med* 2000;132:862-70.
4. Morris CK, Ueshima K, Kawaguchi T, Hildeg A, Froelicher VF. The prognostic value of exercise capacity: A review of the literature. *Am Heart J* 1991;122:1423-31.
5. Mark DB, Shaw L, Harrell FE Jr, et al. Prognostic value of a treadmill exercise score in outpatients with suspected coronary artery disease. *N Engl J Med* 1991;325:849-53.
6. Morise AP, Jalisi F. Evaluation of pretest and exercise test scores to assess all-cause mortality in unselected patients presenting for exercise testing with symptoms of suspected coronary artery disease. *J Am Coll Cardiol* 2003;42:842-50.
7. Bhat A, Desai A, Amsterdam EA. Usefulness of high functional capacity in patients with exercise-induced ST depression to predict a negative result on exercise echocardiography and low prognostic risk. *Am J Cardiol* 2008;101:1541-3.
8. Bourque JM, Holland BH, Watson DD, Beller GA. Achieving an exercise workload of ≥ 10 metabolic equivalents predicts a very low risk of inducible ischemia. Does myocardial perfusion imaging have a role. *J Am Coll Cardiol* 2009;54:538-45.
9. Bourque JM, Charlton GT, Holland BH, Belyea CM, Watson DD, Beller GA. Prognosis in patients achieving ≥ 10 METs on exercise testing: Was SPECT imaging useful? *J Nucl Cardiol* 2011;18:230-7.
10. Duvall WL, Levine EJ, Moonthungal S, Fardanesh M, Croft LB, Henzlova MJ. A hypothetical protocol for the provisional use of perfusion imaging with exercise stress testing. *J Nucl Cardiol* 2013. doi:10.1007/s12350-013-9710-6.
11. Phillips L, Wang JW, Pfeffer B, Gianos E, Fisher D, Shaw LJ, et al. Clinical role of the Duke Activity Status Index in the selection of the optimal type of stress myocardial perfusion imaging study in patients with known or suspected ischemic heart disease. *J Nucl Cardiol* 2011;18:1015-20.
12. Shaw LJ, Mieres JH, Hendel RH, Boden WE, Gulati M, Hachamovitch R, et al. Comparative effectiveness of exercise electrocardiography with or without myocardial perfusion imaging single photon emission computed tomography in women with suspected coronary artery disease: Results from the What Is the Optimal Method for Ischemia Evaluation in Women (WOMEN) trial. *Circulation* 2011;124:1239-49.
13. Bateman TM, Heller GV, McGhie AI, Courter SA, et al. Multi-center investigation comparing a highly efficient half-time stress-only attenuation correction approach against standard rest-stress Tc-99m SPECT imaging. *J Nucl Cardiol* 2009;16:726-35.
14. Chang SM, Nabi F, Xu J, Raza U, et al. Normal stress-only versus standard stress/rest myocardial perfusion imaging: Similar patient mortality with reduced radiation exposure. *J Am Coll Cardiol* 2010;55:221-30.
15. Thompson RC, McGhie AI, Moser KW, O'Keefe JH Jr, Stevens TL, House J, et al. Clinical utility of coronary calcium scoring after nonischemic myocardial perfusion imaging. *J Nucl Cardiol* 2005;12:392-400.
16. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, et al. 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiology Nurses Association, Society for Cardiac Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation* 2012;126:3097-137.