Is there room in the MPI toolbox for another prognostic indicator?

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Over the past 40 years, myocardial perfusion imaging (MPI) has evolved from a primarily planar technique using thallium-201 to first a single-photon emission computed tomography (SPECT) procedure using thallium-201 and later technetium-99m-labeled perfusion tracers and then to a positron-emission tomography (PET) procedure using a variety of tracers such as ¹³N-ammonia and rubidium-82. SPECT MPI technology has progressed from single-head to multi-head rotating gamma cameras systems and in the past 15 years to solid-state non-Anger camera imaging devices. The increased sensitivity and fixed gantry designs of the latter systems have allowed introduction of shorter acquisition times and imaging protocols similar to those used with full-ring PET systems. A challenge for new solid-state camera protocols is that they sometimes diverge from the procedures specified in the labels of approved MPI tracers, which were based on clinical trials using conventional Anger-type gamma cameras. Even guidance from professional societies such as ASNC can become out of date within a few years as a result of the rapid pace of advancements in nuclear imaging equipment technology.¹

Some findings on MPI, such as regional inducible ischemia, reduced coronary flow reserve, and presence of myocardial viability, have direct and often immediate clinical implications. Other MPI findings are more non-specific and may be considered prognostic because of their association with overall coronary disease burden.

Such findings are more often observed on post-stress imaging, including increased lung uptake,^{2,3} left ventricular chamber (LV) dilatation,⁴ and decreased LV systolic function on gated SPECT imaging.⁵ These additional observations are often associated with underestimation of the severity of coronary artery disease on standard segmental perfusion analyses.^{2,6,7}

Ancillary prognostic findings on MPI can be helpful but also problematic. In a patient with known CAD of moderate severity on angiography, such findings can tip the balance toward more aggressive medical or interventional management. However, similar findings in a patient with less severe or no known disease can increase concern for possible microvascular or infiltrative disease that may be difficult to confirm without more invasive procedures. While it is important to identify all abnormal findings on a MPI exam, serving the needs of the patient requires maintaining perspective and placing all observations in the appropriate context.

Regarding identification of stress-induced changes in myocardial perfusion and function, it is logical to expect such changes to be most evident at the time of peak exercise or pharmacological stress. This is the basis for injecting the perfusion tracer at this time, and early experience with thallium-201 confirmed that some perfusion defects seen on imaging within several minutes of injection were no longer identified on repeat imaging 20–30 minutes later.^{8,9} This phenomenon was a particular concern in thallium imaging, in that patient stabilization sometimes necessitated a delay in initiating post-stress image acquisitions. One of the benefits of ^{99m}Tc-labeled perfusion tracers is that myocardial distribution is essentially fixed shortly after injection, such that delay in starting image acquisitions to allow for blood pool and liver activity clearance has minimal effect on perfusion defect detection. However, delay in initiating image acquisition for this purpose may present an impediment to implementing newer protocols that specify earlier imaging start times.

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In the current issue of JNC, Otaki and colleagues present results demonstrating the potential additional value of early post-stress MPI SPECT using a solid-state camera.¹⁰ The study involved 151 patients who underwent rest followed by regadenoson stress ^{99m}Tc-sestamibi imaging. LVEF was determined automatically from 10 to 12 minute upright followed by supine rest acquisitions. The same sequence, with acquisition times of 6-8 minutes, was used for stress imaging, with the supine (“early”) acquisition initiated at 2 minute post-administration of Regadenoson followed by a repeat upright (“late”) acquisition. EF reserve, Δ end diastolic volume (EDV), and Δ end systolic volume (ESV) were calculated as the absolute differences between stress and rest values from the same position. Patients were subsequently followed for a mean 3.2 years for occurrence of major cardiac adverse events (MACE), defined as the composite of all-cause mortality, non-fatal myocardial infarction, unstable angina, or late coronary revascularization. Patients with EF reserve < 0% on the early acquisition (compared to the equivalent supine rest study) had significantly decreased event-free survival. Change in early ESV $\geq$ 5 ml was also associated with decreased event-free survival. Stress total perfusion defect (TPD) was significantly associated with MACE on univariable and multivariable Cox proportional hazards analyses, as were early EF reserve, early Δ ESV, and early Δ EDV $\geq$ 5 ml. Changes in measurements using late post-stress imaging were not associated with differences in event-free survival.

The findings in this report are particularly intriguing because the early post-stress images coincide with the timing of peak vasodilator effect for regadenoson. The further 6-8 minutes that elapsed between the start of the early and late post-stress acquisitions was sufficient to reduce the LV functional impact of the coronary vasodilation such that the relationships of EF and volume changes to MACE were no longer statistically significant. This highlights the difference between the perfusion imaging findings, which demonstrate flow distribution as of the time of radiopharmaceutical administration, and functional parameters from gated images, which change as the physiological effects of the vasodilator wane. Analogous to the potential difference between thallium images at 2 and 30 minutes post-stress, the capability to acquire dynamic images in near real-time of peak vasodilator effect provides an opportunity to detect an additional impact of this stressor which may be missed on images acquired as per the standard protocol for the perfusion tracer.

A critical concern with prognostic information is the manner in which it impacts patient management decisions. As noted earlier, there have been numerous ancillary observations on planar and SPECT MPI that

identified higher-risk patient cohorts. This is consistent with the myriad risk factors for poorer outcomes identified in large prospective trials and retrospective analyses of data from heart disease patients. Nevertheless, knowledge of such greater risk only infrequently translates into specific additional actions to mitigate it. In the current study of older patients (mean age 70) with preserved LV function (mean LVEF 68%), it is unclear how the additional immediate post-stress findings could have been used to reduce MACE risk, especially as a conventional CAD marker (stress TPD) was higher in MACE patients (mean 12 vs 5, $P = 0.0005$). It seems unlikely the higher-risk profile would have affected occurrence of the 6 revascularizations and 9 myocardial infarctions during the follow-up period. The remaining MACE events were all-cause mortality, and as the mean age among MACE patients was 77, at least some of these 13 deaths were likely due to non-cardiac causes. In order to demonstrate that early post-stress measurement of LVEF reserve has “value” as a management tool, larger prospective trials are needed to validate the current findings and examine potential management changes such findings might justify.

The results of this study also raise questions about how best to update technical guidelines to reflect improvements in instrumentation and computer capabilities. Professional societies such as ASNC and ACC usually update guidance on procedures such as MPI periodically but have the discretion to make ad hoc changes in response to new data from major clinical trials. The most recent ASNC guidelines recommend a delay of 15-60 minutes following post-stress administration of ^{99m}Tc-labeled MPI agents (using a conventional Anger gamma camera or a solid-state device), consistent with methods used in the registration trials for those agents.¹ One reason for the delay in starting image acquisitions is to allow clearance of activity from the liver, which reduces image artifacts in the inferior wall. As there are only limited data showing that the earlier post-stress acquisitions used in the present study provide images of satisfactory quality,¹¹ further validation of the proposed new protocol is needed. With such additional evidence, it may be possible to consider earlier post-stress imaging on solid-state cameras as an option for routine clinical MPI procedures.

The great strength of nuclear cardiology imaging is its demonstration of functional behavior at the tissue level. The advent of CZT solid-state camera systems with fixed position detectors has enhanced the capabilities to evaluate processes where there is ongoing change in some attributes of the target organ. While dynamic scintigraphic imaging can track changes in distribution of a radiotracer over time, such as for ⁸²Rb

PET or renal uptake and clearance of ^{99m}Tc -MAG3, gated SPECT MPI with ^{99m}Tc -labeled tracers produces dynamic images based on spatial changes of the essentially fixed distribution of tracer in the myocardium. The present study suggests additional potential for solid-state cameras to be used in exploring dynamic behavior of the myocardium as previously investigated using planar and SPECT-gated blood pool imaging. Regardless of whether measurement of early post-stress EF reserve becomes a routine element of pharmacologic stress MPI, continued identification of additional uses for current and developing imaging technology is important for maintaining the present status and future relevance of nuclear cardiology in clinical patient evaluations.

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