Low-dose stress-only myocardial perfusion imaging

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Since their peak in the 1960s and early 1970s, coronary artery disease (CAD) mortality rates have declined approximately 50%.¹ Much of this progress has been attributed to diagnostic, medical, and interventional technique advancements which have led to improved patient-centered outcomes. Despite these successes, heart disease remains the leading cause of death in both men and women, of which the greatest burden is attributable to CAD.² Critical to the goal of reducing CAD morbidity and mortality further is the use of safe, accurate, data-driven, and cost-effective cardiovascular imaging tools. Proper use of cardiovascular imaging can facilitate (1) earlier diagnosis of CAD, which will improve primary prevention of cardiac events, and (2) risk stratification and prognostic guidance for those with known CAD. For many years, radionuclide myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) and, more recently, positron emission tomography (PET) has served this role.³

In patients at intermediate risk of CAD, the addition of SPECT increases diagnostic accuracy, when compared with ECG stress testing alone, adds prognostic information, and is cost effective.⁴ Numerous prior studies have established that abnormal myocardial perfusion on MPI is associated with future risk of cardiac

events.^{4–6} A normal MPI is associated with annual cardiac death or myocardial infarction rate between 0.7% (exercise) and 1.2% (pharmacological stress), which is roughly similar to population rates of patients without an established diagnosis of CAD.⁷ In contrast, an abnormal MPI is associated with several folds increased risk of cardiac events (as high as 12-fold increased risk in some reports).⁸ Risk stratification is not only important in informing the patients of their future cardiac risk, but serves an important role in guiding treatment strategies that balance cost and risks of therapy with anticipated therapeutic benefit.⁴ Observational data have demonstrated that normal MPI is a strong deterrent to additional confirmatory testing, with only 1% of patients undergoing downstream coronary angiography.^{4,9} Medical decision-making guided by MPI risk stratification is also essential in patients known to have CAD, even when coronary anatomy is known.¹⁰

Due to the widespread use of MPI, its dependence on ionizing radiation has come under increased scrutiny in the scientific community as well as the public media. The radiation-related adverse effects of MPI are stochastic rather than deterministic, with no known safe lower limit of exposure below which there is no possibility of downstream risk of future malignancy.¹¹ It is therefore self-evident that the best approach to reduce radiation exposure due to MPI is to restrict its use to patients who actually need it and would benefit from undergoing imaging. To this effect the American Society of Nuclear Cardiology, in collaboration with other societies, has developed the Appropriate Use Criteria to help support the utilization of cardiovascular imaging in appropriate patients while reducing its use in patients who are unlikely to benefit from it.¹² In this regard, it is important to point out that in appropriate scenarios, the benefits derived by patients from the information provided by MPI far outweigh the risks of radiation exposure (and other risks discussed elsewhere).^{13–15}

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When this distinction is ignored and imaging is curtailed on a widescale (i.e., even in appropriate situations), patients are deprived of the benefits of advanced imaging and the public is put at risk of backsliding on the gains made over the last decades described above. Nevertheless, even in patients who would clearly derive benefits from MPI, numerous advancements have been made with the goal of reducing patient exposure to ionizing radiation including use of lower-dose radioactive agents, stress-only protocols (for normal stress studies), use of higher sensitivity solid-state cameras and multi-detector systems, and use of iterative reconstruction (IR) rather than traditional filter back projection (FBP).¹⁰

Since radiation exposure risk in MPI is stochastic and there is no safe lower limit, the field is governed by the ALARA (As Low as Reasonably Achievable) principle. A direct application of this principle would require the use of the lowest possible tracer dose that will still provide diagnostic quality images. As alluded to above, the best application of ALARA is to avoid radiation exposure altogether when MPI is not needed. An interesting and provocative study by Bourque et al. demonstrated that patients who achieve a workload of 10 or more METs have a very low prevalence of myocardial ischemia on imaging and, more importantly, have a very low rate of cardiac events during follow-up.¹⁶ A recent study by the same group extended these findings to older adults (aged 65 years and older).¹⁷ Based on these data, Duvall et al. developed a provisional protocol in which patients who achieve 10 or more METs during stress testing would not receive the tracer injection and do not undergo imaging.¹⁸ In a prospective study, they demonstrated that the application of this protocol is feasible and that patients who do not undergo imaging have a low rate of events during follow-up.¹⁹ These studies show that the adoption of innovative protocols that avoid imaging altogether in select populations is safe, cost effective, and decreases radiation exposure.

Another protocol that has gained widespread adoption in current practice includes stress-only imaging whereby, in appropriately selected patients with normal stress images, the rest portion of the study is omitted. This omission of rest image acquisition not only saves the patient from exposure to additional ionizing radiation, but compared with traditional stress/rest or rest/stress imaging also has the added benefit of reducing cost as well as the time commitment necessary to undergo an MPI study. Stress-only imaging has been validated in numerous prior studies showing a comparable prognosis for patients with a normal stress-only imaging study as compared to normal traditional stress/rest study.²⁰ A study by Chang et al. in 2009 looked at

outcomes in > 16,000 patients with a median follow-up of 4.5 years, of whom ½ underwent stress-only imaging, and showed that the mortality rate for patients with normal stress-only imaging was similar to patients who had normal traditional stress/rest imaging.²¹

Advancements in hardware design have introduced high-efficiency cameras which replace the NaI-based detectors used in traditional Anger cameras with cadmium-zinc-telluride (CZT) semiconductor-based detectors. These solid-state camera systems have multiple advantages over their traditional Anger counterparts including a compact design that allows for novel detector configurations designed specifically for cardiac image acquisition. They also have the benefit of a three- to five-fold higher photon sensitivity and increased spacial resolution compared to Anger cameras.²⁴ These improvements allow for the introduction of novel imaging protocols with shortened acquisition times and/or radiation exposure and are now in common use in multiple laboratories.²⁵ Importantly, the stress-only protocol discussed above can be used in conjunction with a high-efficiency solid-state camera to further reduce radiation exposure.^{22,23}

Other technological advancements in data processing have made it possible to change how acquired radiation counts are processed in order minimize counts necessary to create diagnostic images. Iterative reconstruction uses mathematical modeling with multiple reconstruction techniques to create computer-generated projections that estimate the distribution of radioactivity created by the imaging source, and then updates the model through multiple iterations to more closely approximate the true distribution.¹⁰ Different iterative reconstruction algorithms such as Wide Beam Reconstruction (UltraSPECT), Evolution for Cardiac (GE Medical Systems), and Astonish (Philips Healthcare) have been used by vendors to improve image quality, decrease imaging time, and decrease tracer dose.²⁶ These algorithms are able to generate SPECT images comparable to traditionally filtered back projection images using radiation count densities of 50%-75% of the typical protocols depending on the software vendor.²⁶

This technology has been validated in studies such as those by Borges-Neto et al. which showed that 17-segment model summed stress scores, summed rest scores, and summed difference scores were not significantly different when comparing full-time FBP and half-time Wide Beam Reconstruction (WBR) protocols in 50 study patients undergoing rest/stress MPI.²⁷ Subsequent studies by DePuey et al. showed that in 156 patients undergoing MPI, half-time WBR resulted in substantially improved visual image quality compared to full-time FBP.²⁸ This study also showed that half-time

ordered subset expectation maximum (OSEM) iterative reconstruction had equally good image quality compared to full-time FBP, though not quite as good as WBR. This ultimately set the stage for additional studies which showed that both half-time and half-dose WBR had better image quality scores than full-time OSEM and FBP without a loss of accuracy or diagnostic certainty.^{26,29,30}

In this issue of the *Journal of Nuclear Cardiology*, Nappi et al. report the results of a single center, single-arm, prospective trial to evaluate outcomes of patients with known or suspected CAD who had a normal perfusion study with a half-dose MPI SPECT stress-only protocol using conventional Anger camera with WBR.³¹ Nappi et al. recruited 2106 patients which were followed up for a mean of 6.6 years looking at outcomes of cardiac death, non-fatal myocardial infarction, and non-cardiac death. Of the 96% of patients who were not lost to follow-up, the overall annual cardiac event rate of cardiac death or non-fatal myocardial infarction was 1.2%, a rate similar to that seen in patients with normal stress-rest MPI and stress-only MPI using regular dose.^{7,21,32} As expected, frequency of cardiac event rates was not homogeneous but varied based on underlying risk factors including age, male gender, diabetes, prior myocardial infarction, and with use of pharmacologic stress testing based on both univariate and multivariate analyses.^{33,34} Indeed, for diabetic males aged > 70.5 years the annual event rate was 6.83% compared to non-diabetics with no prior history of myocardial infarction aged < 64.5 years who had annual event rates of 0.47%.

While prior reports have shown that the picture quality of half-dose stress testing is comparable to traditional MPI for the diagnosis of CAD, there has been limited prospective data to suggest whether or not normal half-dose MPI SPECT carries the same prognostic significance as a traditional full-dose study.^{26,29} The findings by Nappi et al., although limited by the fact that this is a single-arm trial, are indicative of the low risk of cardiac events seen with half-dose MPI SPECT stress-only protocols using traditional Anger cameras with novel software design.³¹ Thus, improvements in software and hardware are possible technological advancements that can lead to improvements in patient safety while maintaining diagnostic and prognostic accuracy.

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