Is SPECT myocardial perfusion imaging on its dying bed?

Fadi G. Hage, MD, MASNC^{a,b}

^a Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

^b Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL

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This is an interesting question to contemplate in the *Journal* dedicated to the field of nuclear cardiology. Nevertheless, it is a question we will consider and try to address since we (all of us at ASNC and beyond who are engaged in the field of nuclear cardiology) do not owe fealty to a modality but are rather fierce advocates of our patients' welfare. Putting the patient first means that we would abandon a given modality if it reached end of life rather than continue to cling on it for personal or sentimental reasons. Now that we have taken that out of the way, let us consider why we are posing the question in the first place.

While single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) remains one of the most commonly used imaging modalities in cardiology, there is no doubt that the volume of studies performed in the USA has dropped significantly over the last 15 years.¹ There are multiple factors that have plausibly contributed to this decline including changing referral patterns and group practices, decreasing reimbursement, and increasing attention to the appropriateness of testing, among others. Aside from the need to curtail cost of imaging, the high—and rising—rate of normal studies over the years which has been documented in multiple studies,^{2,3} raises questions regarding the necessity of performing SPECT MPI (or any testing) in some patients currently referred for the test. Pressure has also mounted from competing imaging modalities, especially coronary computed tomography angiography (CCTA), which have accumulated

increasing evidence supporting their use.⁴ Finally, the publication of the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA)^{5,6} raised questions regarding the utility of SPECT MPI if it will not drive patient management.

SPECT MPI is performed in patients with or suspected of having ischemic heart disease. The readers of the *Journal* need no reminder regarding the wealth of data supporting the use of SPECT MPI that has been accumulated over decades and is unparalleled by any imaging modality in the field of ischemic heart disease.⁷ Other testing modalities that are used to evaluate for ischemic heart disease include exercise ECG, stress echocardiography, and stress magnetic resonance imaging, among others. Exercise ECG is a good screening test in some patients who have a normal ECG and are able to exercise to a meaningful level but has lower sensitivity and specificity compared to imaging. Stress echocardiography is attractive to perform in low risk patients due to its wide availability and lower cost but its sensitivity for detection of ischemia is lower than SPECT MPI. One thing to consider is that the assessment for myocardial ischemia with SPECT MPI is at peak stress while with exercise echocardiography it is generally not at peak stress especially when treadmill is used. When exercise is not an option, dobutamine echocardiography is less attractive due to the length and complexity of the protocol (compared to vasodilator SPECT MPI) and the higher rate of side-effects.⁸ Stress magnetic resonance imaging has limited availability. A main attraction of these modalities, compared to SPECT MPI, is the absence of ionizing radiation. While all these modalities have legitimate uses in particular patients, it is unlikely that any one of them will replace SPECT MPI to a significant effect due to the mentioned limitations. That is not to say that these modalities will not continue to grow and have a complimentary role in the management of specific subsets of patients.

Reprint requests: Fadi G. Hage, MD, MASNC, Division of Cardiovascular Disease, Department of Medicine, University of Alabama at Birmingham, LHRB 326, 701 19th Street South, Birmingham, AL 35294; fadihage@uab.edu
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An alternative approach to the evaluation of patients with ischemic heart disease is to assess the presence of significant stenosis in the coronary arteries—the anatomic approach. While an anatomic evaluation of the coronary arteries is feasible with invasive angiography, most agree that a more rational approach would involve a non-invasive gateway to avoid the complications associated with this approach in patients who are unlikely to have significant coronary artery disease. With the maturation of CCTA it is now possible to anatomically evaluate the coronary arteries non-invasively, at least in the proximal portion of these arteries. Advantages of CCTA over SPECT MPI include a higher diagnostic accuracy when invasive angiography is used as gold standard, its excellent negative predictive value (with same gold standard), and rapid nature of the test. Some disadvantages include use of nephrotoxic contrast and limited image quality with high heart rate, coronary calcification, and coronary stents. It has also been noted that CCTA leads to more downstream invasive coronary angiography compared to functional testing without an improvement in clinical outcomes.⁹ Nevertheless, CCTA is an exciting modality that in the right patient will allow the rapid rule-out of coronary artery disease or the confirmation of the presence of disease leading to the initiation or intensification of appropriate medical therapy.

One limitation of the anatomic approach is its inability to determine the functional significance of a coronary stenosis. Similar to the use of functional flow reserve (FFR) in the catheterization laboratory to address this issue, FFR by CCTA allows for the non-invasive functional assessment of a coronary lesion. This methodology uses fluid dynamics analysis to estimate FFR from the CCTA images; therefore, a prerequisite is the availability of high quality CCTA images. It is important to note that on a fundamental level this remains an anatomic assessment rather than a functional assessment. We now appreciate that coronary artery disease is only one factor in the development of ischemic heart disease and that a substantial proportion of patients have other causes of myocardial ischemia.¹⁰ Patients with angina/myocardial ischemia without obstructive coronary artery disease are at increased risk of cardiac events.¹¹ This has intensified the interest in coronary microvascular disease, which due to the limitation of current technology can not be assessed using an anatomic approach and requires functional testing to determine its presence.¹² Note that in this subset of patients CCTA (with or without FFR by CCTA) will be false negative.

The non-invasive gold standard for the assessment of myocardial blood flow, and coronary microvascular disease, is positron emission tomography (PET) MPI.

PET MPI can be considered as an upgrade of SPECT MPI, just as SPECT MPI was an upgrade of planar MPI. PET uses higher energy photons than SPECT (511 KeV vs. 140 KeV for Tc-99m) and has a higher count sensitivity resulting in studies with higher overall counts and better spatial resolution than SPECT MPI. The PET tracers have shorter half-lives and lower radiation exposure compared to SPECT, and PET MPI protocols are generally shorter than SPECT MPI protocols especially if the study requires both stress and rest imaging. Unlike SPECT MPI, PET MPI is always attenuation-corrected and the attenuation-correction is more robust than with SPECT MPI since it is depth independent. Finally, and perhaps most importantly, PET MPI allows dynamic imaging to quantify in absolute terms myocardial blood flow, which is a significant advantage over current SPECT MPI. Despite its superiority over SPECT MPI, PET MPI has several disadvantages: PET cameras are not as widely available as SPECT cameras limiting access; PET cameras are significantly more expensive than SPECT cameras; currently available PET tracers have short half-lives requiring cameras to be located in physical proximity to a cyclotron or the acquisition of an expensive generator that requires routine replacement; PET tracers are more expensive than SPECT tracers; interpretation requires familiarity with CT scan or collaboration with another reader to assess for the presence of incidental findings. Therefore, while PET MPI provides tangible advantages over SPECT MPI, it is unlikely that it will replace SPECT MPI for routine imaging of myocardial perfusion in the near term. It is very likely that PET MPI volumes will continue to grow and be used in preference to SPECT MPI in select patients, especially when there is clinical need to determine absolute myocardial blood flow. When the above limitations are addressed, the legacy of SPECT MPI will continue in its immediate descendant.

We now consider how ISCHEMIA trial will affect SPECT MPI. While the trial was not a study of SPECT MPI, there is a wide perception that it will negatively influence the performance of functional testing. The trial randomized 5,179 patients with moderate or severe ischemia to an initial invasive strategy with angiography and possible revascularization when feasible on top of medical therapy or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed. The trial is generally misperceived to be a negative trial. In fact, patients assigned to the invasive strategy had greater improvement in symptoms (with the caveat that more than one-third of the patients were asymptomatic at baseline!).⁶ The primary efficacy endpoint (a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest)

was not different between the two groups (hazard ratio 0.93, 95% CI 0.80-1.08, $P = 0.34$) but the event curves crossed at around 2 years, with higher rate of early (peri-procedural) events in the invasive arm and lower risk after 2 years in that arm suggesting that longer term follow-up may show an advantage of the invasive approach.⁵ Indeed, the risk of non-procedural myocardial infarctions was lower in the invasive arm (adjusted hazard ratio 0.67, 95% CI 0.53-0.83). The trial has many caveats: its findings apply only to the type of patients that were included in the trial; lack of generalizability due to slow enrollment, including patients with no symptoms, including patients with no or mild myocardial ischemia, including patients with evidence of ischemia only by ECG, and changing the primary endpoint midway through the trial. The lack of generalizability of the trial was recently highlighted by Al-Mallah et al. who demonstrated that of 709 patients with moderate-to severe ischemia on SPECT MPI at a single center, more than two-thirds had at least one ISCHEMIA trial exclusion criteria.¹³ While ISCHEMIA trial demonstrates the feasibility of a conservative approach in patients with stable angina and myocardial ischemia (when they meet its inclusion/exclusion criteria), it should not detract from the prognostic value of functional testing and its importance to guide therapy in symptomatic patients. MPI is a test that determines the presence, severity, and extent of myocardial ischemia which may or may not be due to coronary artery disease (see discussion above), so it should not be thought of as solely a gateway for coronary revascularization. The information provided by MPI is not available on anatomic assessment, a fact that was recently rediscovered but has been known for 30 years.¹⁴

Finally, we can not ignore the tremendous improvements in SPECT hardware, software, and protocols that have occurred which have greatly improved its relevance to today's practice. These improvements have resulted in enhanced image quality, shorter imaging time, lower radiation exposure, greater sensitivity and specificity for detection of myocardial ischemia, and opened the way for quantitation of absolute myocardial blood flow by SPECT MPI in a manner similar to PET MPI. In addition to these advancements, greater attention to maintaining quality imaging in our laboratories, a task currently spearheaded by ASNC, will help keep SPECT MPI relevant in the current era. The decrease in volume of SPECT MPI studies that we have witnessed over the last few years can be a stimulus to push the field of nuclear cardiology forward. As pointed earlier, some of the studies performed for the assessment of ischemic heart disease (not only with SPECT MPI but also with all the other modalities) may be inappropriate and no testing may be a better strategy in some patients. Despite

these decreasing numbers, SPECT MPI is by far the most frequently performed test for evaluation of ischemic heart disease. Our focus should be on quality and access and not on numbers as it has rightly been since the inception of ASNC. It is indeed remarkable that an imaging test that was born almost 50 years ago¹⁵ is not only alive and well today but is still thriving and will be relevant to the care of our patients for the foreseeable future.

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