DEBATE ARTICLE

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PET should not replace routine SPECT MPS for the assessment of patients with known or suspected CAD

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INTRODUCTION

Single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy (MPS) has been widely available for decades and has been extensively validated for the diagnosis and risk assessment of patients with known or suspected coronary artery disease (CAD).[1,2] It has a class I indication in both US and European guidelines.[3,4] The major part of this validation has been against invasive coronary angiography, largely reflecting the anatomical thinking historically prevalent in cardiology practice. The sensitivity and normalcy of SPECT MPS for the detection of angiographically defined significant CAD is 85%-90% and 89%, respectively,[2] although lower figures are not uncommon in studies subject to post-test referral bias or where the images are interpreted in the absence of the usual clinical information. When compared with invasive coronary angiography with fractional flow reserve, sensitivity is maintained but specificity is lower (61%).[5] Regardless, the prognostic value of normal MPS is well recognized, with an annual coronary event rate <1%.[6] Although such patients may be further stratified by anatomical tests such as invasive or CT coronary angiography, patients with a normal study can usually be reassured without the need for further testing. Those with abnormal MPS have a seven-fold higher annual risk of myocardial infarction and death compared with those with normal studies[7] and the coronary event rate increases with ischemic burden.[6]

Virtually every modern test for myocardial ischemia has been validated at some stage against SPECT. It is widely available, relatively cheap and, above all, cost-effective in a wide range of clinical scenarios.[1,8–10] However, in common with all tests that evaluate myocardial perfusion, SPECT MPS has disadvantages. Spatial and temporal resolutions are lower than for other tests, although iterative reconstruction, resolution recovery algorithms, and solid-state gamma cameras offset these limitations. Although the lower energy of the emitted gamma photons makes SPECT MPS susceptible to artifact from scatter and attenuation, this too can be offset by scatter and attenuation correction.[11] However, an important disadvantage of qualitative SPECT MPS is that the images show relative myocardial perfusion and it is assumed that the area with highest counts represents normal perfusion. In the setting of globally reduced perfusion, this may not be the case and global inducible ischemia can be underestimated or in rare cases may not be apparent at all. These disadvantages may explain in part the performance of SPECT MPS in modern comparisons with other techniques such as CMR[12] and fractional flow reserve.[5]

Positron emission tomography (PET) MPS has many of the virtues of SPECT and it is often considered to be superior because of its spatial resolution and the ability to quantify perfusion in absolute terms. However, proposing PET as a routine replacement for SPECT requires several questions to be answered:
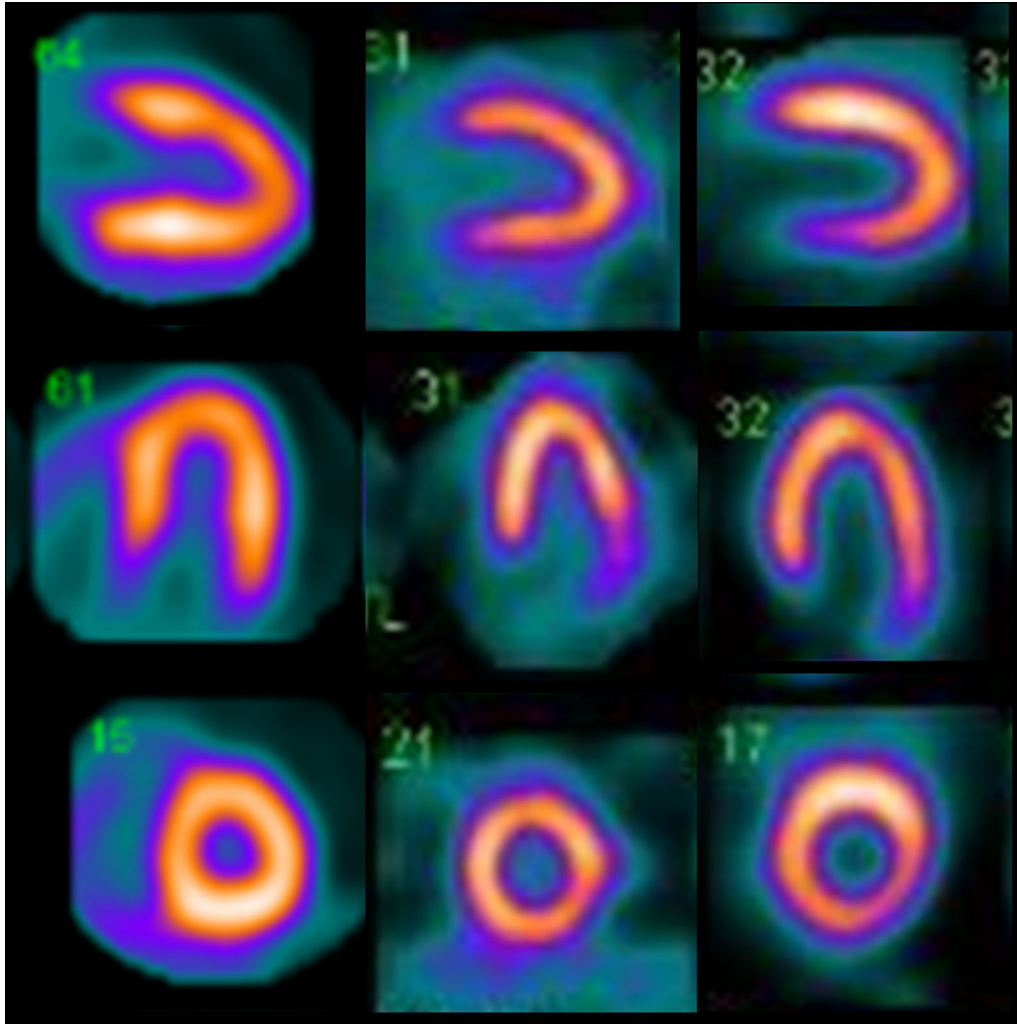
1. Which PET tracer is a realistic choice for widespread use?
2. How does this tracer compare with SPECT?
3. What are the costs of running a PET MPS service?
4. What technological advances for SPECT might address its currently perceived shortcomings?

Figure 1. MPS images from three different patients using thallium-201, technetium-99m-tetrofosmin, and rubidium-82. The SPECT images were acquired using a solid-state camera. Can you guess which tracer is which? Answer: rubidium-82 (*left*), thallium-201 (*center*), technetium-99m (*right*).

WHICH PET TRACER IS A REALISTIC CHOICE FOR WIDESPREAD USE IN MPS?

The ideal PET perfusion tracer is generally said to be ^{15}O-water. It is freely diffusible across the myocyte membrane and it has a net extraction fraction of 100% that is linear across the usual range of myocardial perfusion, including hyperemia. Unfortunately, its half-life is short (120 s) and it requires an on-site cyclotron, which involves additional complexity and expense. ^{13}N-ammonia also requires an on-site cyclotron but it has a more favorable half-life of ∼9 minutes, although a poorer first-pass extraction fraction (80%) and a non-linear relationship between uptake and hyperemic perfusion. These tracers are therefore limited to large, tertiary PET centers with high-volume cardiac and non-cardiac workloads and neither tracer allows PET to replace SPECT as the default for MPS in most centers.

Rubidium-82, injected as rubidium chloride, is a generator-produced PET tracer that is more widely applicable. The parent radionuclide, [82]Sr, has a half-life of 26 days, allowing a single [82]Rb generator to last for several weeks. [82]Rb MPS has been validated for the diagnosis of obstructive CAD and is as sensitive but more specific than SPECT MPS.[13,14] Accordingly, [82]Rb offers the only current realistic choice of tracer if widespread adoption of PET MPS was to be recommended.

Fluorine-18 flurpiridaz has shown excellent characteristics in phase 2 studies but it is not yet commercially available, let alone at a known price, and it need not be discussed further at the moment.[15]

HOW DO THE IMAGING CHARACTERISTICS OF ^{82}RB COMPARE WITH THOSE OF THE SPECT TRACERS?

As with ^{201}Tl, ^{82}Rb is a potassium analog that is taken up both passively and actively into the myocyte. Its extraction fraction decreases non-linearly with increasing perfusion and its uptake characteristics are similar to the ^{99m}Tc agents but poorer than ^{201}Tl. As such, ^{82}Rb offers no advantages over the SPECT MPS tracers in terms of myocardial uptake kinetics.

It is widely believed that PET provides higher resolution images than SPECT because of the physics of coincidence detection of the two 511 keV photons that are emitted when the positron annihilates with an electron. In reality, this is not so because the distance traveled by the positron before annihilation is dependent on its energy and ^{82}Rb emits a particularly high energy positron. The positron range before annihilation is 8.6 mm for ^{82}Rb, 4.1 mm for ^{15}O, 2.5 mm for ^{13}N, and 1 mm for ^{18}F leading to spatial resolution greater than the 5-7 mm that is usually quoted for PET.[16] In practice the resolution of a ^{82}Rb image is no better than that of ^{99m}Tc or ^{201}Tl images acquired using a solid-state camera (see Figure 1).

Second, the half-life of ^{82}Rb is short (75 s) and, with a typical 8-minute cardiac acquisition, the activity remaining at the end of acquisition is only 3% of the injected activity. This requires a large correction factor that proportionally amplifies noise over signal and can compromise the assumptions made during quantification.

Nonetheless, quantification is the most important benefit of PET MPS although dynamic SPECT MPS is now practiced in some centers and compares favorably with ammonia PET for quantification.[17] The problem caused by qualitative imaging is uncertain. Non-regional markers of ischemia such as hemodynamic and ECG changes, post-stress LV stunning, transient RV prominence, and lung activity often flag when qualitative SPECT may be underestimating ischemia.[18,19] In a recent study, only 3 of 580 (0.5%) patients with normal SPECT MPS who went on to have invasive coronary angiography had high risk coronary artery anatomy without predictors on SPECT MPS.[19]

WHAT ARE THE COMPARATIVE COSTS OF SETTING UP AND RUNNING A PET MPS SERVICE?

Even if it were practical to replace SPECT with PET MPS, the cost-effectiveness of such a change has not been established and it is proving hard to persuade payers to make such a change. A cardiac-enabled PET-CT camera costs in the region of $2 million, up to 5 times more expensive than a cardiac-dedicated SPECT camera. Solid-state SPECT is more expensive but it is still only approximately one-third of the price of PET-CT. ^{82}Rb can only become equivalent to the price of ^{99m}Tc-tracers in very high-volume centers with a generator costing in the region of $30,000 and lasting just one month, meaning that at least 500 patients are required each month for the cost of ^{82}Rb to approach that of the SPECT tracers.[20] Few if any centers worldwide have this volume of referrals even if it could be accommodated in a single camera.

In contrast, the cost-effectiveness of SPECT MPS is well known.[8,10] The UK National Institute of Healthcare and Clinical Excellence (NICE) found diagnostic strategies involving SPECT MPS to be more cost-effective than those without.[10] PET MPS was not included in this evaluation but comparisons with SPECT do exist, albeit in different healthcare economic environments.[13,21] Although PET may reduce downstream testing and expenditure compared with SPECT,[13] it is not overall cost-effective.[21]

ADVANCES IN SPECT TECHNOLOGY

The majority of comparisons between SPECT MPS and other coronary functional tests use gamma camera technology developed originally in the 1950s, and may not take advantage of advances such as iterative reconstruction, resolution recovery, and attenuation correction.[12,13] Even with these improvements, the fundamental deficiencies of the Anger camera remain, namely low detector sensitivity and the requirement for photo-multiplication. Solid-state technology has brought improvements that promise to rejuvenate SPECT imaging in general both for cardiac and now for non-cardiac applications. Two cardiac cameras are currently available commercially, DSPECT (Spectrum Dynamics Inc) and the Discovery NM530c (General Electric Healthcare), with both offering improvements in spatial and energy resolution and the capability to reduce imaging time, injected activity, or both. Stress-only imaging with technetium-99m tracers is now feasible at an effective dose of <2 mSv,[22] which compares favorably with the effective dose from ^{82}Rb PET MPS. The spatial resolution of these systems is in the region of 5 mm, which is better than with ^{82}Rb.

CONCLUSION

While accepting that PET MPS using ^{13}N-ammonia or ^{15}O-water provides better quality images and quantitative information compared with conventional SPECT, the need for an on-site cyclotron means that these agents are unlikely ever to be widely adopted. We,

like others, are currently using [82]Rb PET in selected patients but its imaging characteristics are only slightly better, if at all, than SPECT especially if using a solid-state SPECT camera, and its cost-effectiveness is unproven. There is unquestionably a role for PET MPS in high-volume specialist centers such as our own and that of our opponents, but PET should not replace SPECT as the default form of MPS in most centers around the world. Far better to invest in making high-quality SPECT available for all patients who require coronary functional imaging than to adopt the more expensive technology on the assumption that more money buys better outcome for our patients, as opposed to for ourselves.

Disclosures

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