The evolving role of molecular imaging for coronary artery disease: where do we stand today?

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ABSTRACT

The landscape of cardiac imaging is changing rapidly. There are promising new developments in molecular imaging on the horizon. It is likely that nuclear cardiology will continue to play an important role in the evaluation of CAD, but that role must evolve to meet clinical needs, competing technologies and the increasing emphasis on ensuring that imaging adds value and improves outcomes. This review offers some suggestions on the optimal role nuclear imaging can play vis-à-vis alternative options such as CT, but more data are needed before definitive recommendations can be made. Randomised trials comparing different diagnostic strategies can and should be performed to strengthen the foundations of clinical practice in nuclear cardiology. An evidence-based approach to imaging is here to stay.

Myocardial perfusion imaging (MPI) is probably the most widely used test for the non-invasive diagnosis of coronary artery disease (CAD) today in the USA. From 1993 to 2001, Medicare data documented a nearly threefold increase in imaging stress tests,[1] with MPI being the most commonly performed test; over a million MPI studies were performed in 1996, almost twice as frequently as the stress ECG and almost three times more often than stress echocardiography.[2] There are no data on test utilisation in Asia, but in Singapore, the pattern of utilisation appears similar; our institution performs about 7000 studies per year, more than twice the number of ECG exercise stress tests and stress echocardiograms.

Despite this rapid growth in demand, the role of conventional single photon emission computed tomography (SPECT) imaging for CAD is currently undergoing reappraisal, for a number of reasons. First, alternative modalities such as cardiac CT have attracted great interest.[3] With high sensitivity and specificity for detection of coronary artery disease, and a high negative predictive value for ‘‘ruling-out’’ disease, CT is being discussed as an alternative test to myocardial perfusion imaging. The focus on CT has also thrown a spotlight on radiation safety.[4] Second, there has increasing concern in the USA about the costs of healthcare, with cardiac imaging, and MPI being one of the biggest growth areas.[5] There is concern about the possible overuse of testing, and appropriateness guidelines for imaging procedures have been developed, including for MPI[6] and CT.[7] Third, there has been the realisation that assessing the value and benefit of an imaging test requires more than evaluating sensitivity and specificity. Ideally, the benefits of any test should be evaluated in a randomised clinical trial comparing one diagnostic strategy with another, in the same way that randomised clinical trials are performed to evaluate the value of specific interventions in clinical care. One might call this ‘‘evidence-based imaging.’’ Finally, promising new advances in SPECT technology are on the horizon.[8] This review article will offer a reappraisal of the role of nuclear cardiology in the light of these developments. Given that there are many competing technologies for the assessment of CAD (stress echo, CT, PET, conventional nuclear MPI, MRI), we will focus not only on nuclear cardiology but also on how it stands in comparison with alternative techniques.

IMPACT OF NEW IMAGING MODALITIES

There seems to be little debate today regarding the relative merits of MPI versus stress echocardiography; both modalities are well established, with clinical use depending much on availability on expertise and resources. Cardiac MRI, long touted as the ‘‘one-stop shop’’ modality, has yet to fulfil predictions that it would supplant stress imaging by nuclear or echo techniques. However, interest in cardiac positron emission tomography (PET) and, more recently, CT angiography for CAD detection has attracted considerable interest, with a rapid rise in the number of CT studies performed in the USA.[4] Although accurate statistics are not available, informal surveys suggest that many countries in the Asia-Pacific region have seen a similar interest, with CT often adopted as an alternative test to stress testing or stress imaging. Intuitively, the idea of directly imaging the coronary arteries is attractive, especially given the current limitations of stress imaging, which detects only physiologically significant coronary stenosis. The initial results of single-centre 16–64 slice studies were promising, with a meta-analysis[9] of 29 studies involving 2,024 patients reporting per patient sensitivity and specificity ranging from 86% to 100% (mean 95%) and 35% to 100% (mean 74%) respectively. More recent multicentre studies[10 11] of 64 slice scanners have reported sensitivities of 85–95% and specificities of 83–90%. How does this compare with MPI? A summary[12] of 33 studies of exercise myocardial perfusion imaging involving 4480 patients reported sensitivity ranging from 71% to 96% (mean 87%) and specificity from 36% to 100% (mean 73%). These figures overlap substantially with the reported accuracies of CTA, making it difficult to be confident of the superiority of one technique over another. However, in one study of 114 patients who underwent both CT and MPI, 45% of patients with an abnormal MSCT had abnormal MPI; even in patients with obstructive CAD on MSCT, 50%

still had a normal MPI, suggesting that CT has higher sensitivity for detection of atherosclerosis than MPI.[13] This is not perhaps a surprising finding, given that CT is able to detect non-flow-limiting disease as manifested by coronary plaque, which may precede the development of obstructive disease. More head-to-head comparisons of CT and stress imaging are needed to assess diagnostic accuracy. The results of the ongoing SPARC study[14] (Study of Perfusion and Anatomy's Role in CAD), an open-label multicentre registry comparing clinical outcomes of patients undergoing four different diagnostic strategies (stress SPECT, stress PET, CT angiography and PET-CT), will help to address this question.

Given the wide variety of alternatives for diagnostic testing (stress ECG, stress echo, PET, MRI and CT), when is SPECT a preferred test? Apart from issues of availability, cost and expertise, it is helpful to consider the clinical scenario and the pretest likelihood of disease, which has major impact on the post-test probability of disease, the proper interpretation of a test result and the value of a test.[15]

For example, in patients with a *very high likelihood* of coronary artery disease, such as a diabetic with typical symptoms and a positive stress ECG test, the recommended test is invasive coronary angiography, since this is needed for intervention whether PCI or CABG. There is little role for CT angiography in this setting, and this is reflected in the guidelines.[7] If coronary angiography is not planned, the guidelines rate stress MPI as appropriate and useful in the risk stratification of patients following acute coronary syndromes.[6] A number of studies, including the multicentre INSPIRE study[16] have repeated demonstrated the value of MPI in this setting.

Conversely, for *low-risk, asymptomatic* patients without any suspicion of CAD, the guidelines do not currently recommend unselective screening by either perfusion imaging[6] or CTA.[7] There has been interest in using MPI as a screening tool in asymptomatic diabetics, with the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study[17] indicating that 22% of asymptomatic diabetics had evidence of ischaemia. However, preliminary data from this study have been recently presented, suggesting that there was no difference in long-term outcome between patients randomised to screening by MPI versus standard care. The potential role of screening using CT was studied in a recent report of 1000 asymptomatic Korean patients undergoing CTA.[18] Two per cent of patients had evidence of ≥75% stenosis of a coronary artery. Based on these data, the authors did not recommend routine screening for CAD using CTA. Guidelines consider calcium scoring[19] a reasonable adjunct in the overall risk assessment of the patient with a intermediate risk (10–20% 10-year risk of CAD by Framingham score) since an elevated score might reclassify the patient into a higher risk category. To summarise, current guidelines do not support unselective screening of asymptomatic individuals for CAD using either MPI or CT. There may be a role of selective use of calcium scoring in asymptomatic patients at intermediate risk, if it is likely to change the patient's risk assessment and subsequent management.

Diagnostic testing has its greatest value for patients in the *intermediate likelihood* category, where a normal or abnormal test can shift the patient's probability of disease into a high- or low-risk group. Examples of such situations would be patients with atypical symptoms and equivocal ECG stress tests, or asymptomatic patients with positive stress ECGs. Traditionally, MPI or stress echo has been used in this setting, particularly if the patient is unable to exercise adequately or has an abnormal resting ECG. However, CT angiography can be considered as an alternative, especially if patients have a low to intermediate likelihood of CAD,[3] and the likelihood of a normal result is relatively high. The advantage of using CT angiography as an alternative for such patients is its negative predictive value; a normal result should virtually rule out the possibility of CAD, offering much reassurance and avoiding the need for further testing. On the other hand, should a CTA be severely abnormal, suggesting the presence of severe disease, coronary angiography might then be considered, especially if the patient is symptomatic. However, one disadvantage of CT is the presence of calcium in patients with advanced disease, and its limited resolution, so that there is sometimes uncertainty regarding the physiological significance of a stenosis, necessitating further testing with stress imaging.[20] Thus, a proportion of patients undergoing CT require further stress testing before a decision can be made on coronary angiography, and the numbers of such patients might be expected to increase with the likelihood of disease. Indeed, one study has suggested that the diagnostic accuracy of CT angiography is greatest in patients with low to intermediate likelihood of CAD but might be less than optimal in patients with a high likelihood of disease.[21] Thus, if the likelihood of CAD is higher (for example, an elderly diabetic with multiple CAD risks), it may be preferable to perform stress imaging. A highly abnormal SPECT result indicating severe ischaemia would result in a recommendation for angiography, while a mildly abnormal result (mild ischaemia) could be approached with medical therapy.[20] The ability of SPECT MPI to risk-stratify patients and identify those who will benefit from revascularisation is well established. In an observational study of over 10 000 patients who underwent MPI, patients with significant ischaemia (>10% of the left ventricle) were shown to benefit from revascularisation, whereas those without significant ischaemia did better with medical therapy.[22] Another large observational study, the Economics of Non-invasive Diagnosis (ENDS) compared the outcomes from a strategy of direct invasive angiography for management of CAD against a strategy of selective angiography based on detection of ischaemia by MPI[23] in 11 372 patients. The authors showed that the outcomes of the selective approach based on MPI appeared equivalent or better than the unselective approach of direct invasive angiography, and the MPI-based approach was associated with lower long-term overall costs. More recently, the landmark COURAGE trial did not show any survival advantage of a strategy of immediate percutaneous intervention (PCI) over deferred, selective PCI based on symptoms,[24] but the results of the COURAGE nuclear substudy[25] were consistent with earlier studies demonstrating that MPI was able to identify patients who would benefit from revascularisation. To summarise, the choice of test depends on the likelihood of disease; for patients with a high likelihood of CAD, MPI may be preferable because of its ability to risk-stratify patients, and identify those more likely to benefit from revascularisation, whereas for patients with a low to intermediate likelihood of disease, CT may be a good alternative test because it is an excellent test for ruling out CAD. This position appears to be reflected in appropriateness guidelines[7] and expert opinion.[3 20]

For patients with known CAD, for example, prior infarct or prveious revascularisation, the situation is different. For such patients, the diagnosis of CAD is not in question; rather the issue is whether there is ischaemia, restenosis, viability or progression of disease in either native vessels or grafts. For patients with a prior infarct, MPI and stress echocardiography have established roles with many studies demonstrating their value, including the recently published INSPIRE study.[16] For the assessment of myocardial viability, both SPECT and echocardiography are widely used, and cardiac MRI with late gadolinium enhancement, or PET is an excellent alternative. In contrast, there are limited data for CT in this setting although much research interest in the potential of CT to evaluate perfusion and viability with late contrast enhancement. There has also been intense interest in CTA for detection of stent restenosis. While emerging data are encouraging,[26] this indication is rated as "uncertain" in appropriateness guidelines for use of CT.[7] For patients with prior bypass grafts, CT is excellent at assessing graft patency[27] but may not be optimal for evaluation of native vessels, given the usually advanced state of native disease in such patients. The appropriateness guidelines[7] for CT rate its role in this setting as "uncertain." In contrast, SPECT MPI is able to provide a "global" view of the state of perfusion, presence of ischaemia and/or viability in patients with prior revascularisation who develop symptoms, and appropriateness guidelines have assessed the use of SPECT in this setting as appropriate.[6] These recommendations may evolve with technical advances in CT.

To summarise, MPI (and stress echocardiography) continues to have an important role in the risk stratification of patients with CAD, especially patients with an intermediate to high likelihood of disease who are not candidates for immediate angiography. The strength of CT is in the lower likelihood group of patients (for example, a younger patient with atypical symptoms, minimal risk factors, equivocal stress testing), where a negative result will be excellent for ruling out CAD. CT also has strengths in evaluating patients with suspected coronary anomalies, cardiac masses and graft patency, especially prior to redo bypass surgery.

COMBINING INFORMATION FROM SPECT AND CT

Rather than seeing stress imaging and CT as competitive tests, it is helpful to consider that the information provided by these tests is often complementary and additive. A number of studies have addressed this. First, although calcium scores have been shown to correlate with MPI studies, with the likelihood of abnormal MPI increasing with the score, less than 50% of patients with elevated scores above 400 have abnormal MPI scans, indicating that extensive atherosclerosis is possible without the presence of myocardial ischaemia.[28 29] Of note, a normal SPECT study confers an excellent prognosis despite the presence of high calcium scores.[30] A recent PET-CT study also showed that calcium provided additional information on prognosis to PET MPI studies.[31] These data suggest that the anatomical information provided by calcium scoring and the perfusion and function information provided by MPI with either SPECT or PET are indeed complementary. When should a patient undergo both tests, then? Although more studies are needed, it might seem logical to perform stress imaging in patients with a high calcium score, since the prognosis of such patients appears to be relatively benign if the SPECT study is normal.[30] One study has shown that calcium scoring appears to add value to SPECT by enhancing accuracy for detection of CAD,[32] so that when a calcium score was added to SPECT, the sensitivity for detection of CAD increased from 76% to 86%, without a significant fall in specificity. Thus, in a patient with suspected CAD but a negative SPECT study, calcium scoring may add value by detecting atherosclerosis.

Given the potentially synergistic value provided by anatomical and functional information, there has been much interest in developing hybrid scanners, combining either SPECT or PET with CT scanning. PET-CT is already a well-established clinical tool in general nuclear medicine, particularly for oncology work. The combination of PET with CT in a hybrid scanner is logical and synergistic for cancer imaging, since PET has a high sensitivity for lesion detection, and CT is excellent for localisation and provides attenuation correction. For cardiac work, a 16 or 64 slice scanner would allow for imaging of both the coronary arteries and perfusion in a single machine, with fusion of images to allow for accurate correlation of the vascular territory with the area of ischaemia on PET. There are many advantages to this approach,[33] but bearing in mind the higher cost of PET scans, more studies such as SPARC[14] are needed to determine if such an approach is cost-effective or provides additional diagnostic value over conventional SPECT, PET or CT alone. There has also been interest in SPECT-CT scanners for nuclear medicine purposes; these have the advantage of lower operating costs compared with PET-CT. However, the radiation exposure from a combined SPECT-CT study is relatively higher than for a PET-CT cardiac study.[34] An alternative approach is to perform image fusion from stand-alone SPECT and CT studies in selected patients, where there is uncertainty about the culprit vessel on abnormal MPI studies. Gaemperli *et al*[35] found that, in 29% of patients with at least one perfusion defect on SPECT, fusion of CT and SPECT images was able to provide confirm or exclude the haemodynamic significance of the suspected culprit vessel, providing information that would not be available without fusion of images.

Radiation safety

The growth of CT has highlighted the issue of radiation safety. The main concern is the potential of radiation to give rise to subsequent cancer, a theoretical risk that is difficult to quantify. One study has estimated the incremental lifetime risk of cancer as a result of exposure to 10 mSv of radiation (a typical 64 slice cardiac CT study might expose patients to this amount of radiation) at approximately one per 1000 subjects for a 40-year-old man.[36] This risk would be substantially higher in a young woman and much lower in an elderly man. Newer ECG triggered protocols are able to reduce the radiation exposure. Although less often emphasised, SPECT studies might expose patients also to comparable amounts of radiation, ranging from 10 to 12 mSv for a same-day rest–stress Tc-99m-based study, to higher doses for thallium studies and lower doses for separate day Tc-99m scans.[37] For a symptomatic patient with suspected CAD, these risks might be considered relatively small, especially when compared with the potential benefit of the additional diagnostic information provided by imaging. However, in a screening situation, the potential benefit is much smaller and might be offset by the risks of exposure.

APPROPRIATENESS GUIDELINES, RANDOMISED TRIALS AND EVIDENCE-BASED IMAGING

Many eminent cardiologists have raised concerns about the likelihood of a healthcare funding crisis in the USA[38 39] due to the growing burden of medical care. One of the major contributors to spiraling healthcare expenses is the rising volume of cardiac imaging procedures. These concerns have prompted the publication of appropriateness guidelines for cardiac imaging for SPECT,[6] CT and MR[7] and echocardiography. One study in an academic medical centre showed that 14% of stress SPECT studies and 18% of stress echocardiographic studies were deemed inappropriate by these standards.[40] It is likely that healthcare providers will place increasing emphasis on the need to audit and evaluate the appropriateness of test utilisation in coming years.

While appropriateness guidelines are essential, they are limited by available evidence and based, to some extent, on expert opinion. One of the recognised strengths of nuclear cardiology is the extensive literature describing its value in a wide range of clinical situations.[41] However, there is an increasing realisation that observational data and studies evaluating diagnostic accuracy are not a substitute for randomised clinical trials. For example, the role of nuclear imaging for preoperative risk stratification was well accepted for many years, based on observational data describing the prognostic value of SPECT for predicting postoperative events. Recent randomised clinical trials have, however, questioned the value of coronary revascularisation prior to major non-cardiac vascular surgery[42] as well as any benefit from preoperative diagnostic testing in high-risk patients who had been beta-blocked.[43] Similarly, PET is widely accepted as having a higher accuracy for detection of viability compared with conventional SPECT imaging, based on observational studies of comparative sensitivity and specificity. However, a randomised trial comparing a SPECT based diagnostic strategy with a PET-based approach was unable to detect a significant difference in clinical outcomes.[44] These findings underline the need to place more emphasis on prospective randomised controlled trials before assuming clinical benefit for diagnostic imaging. Indeed, there has been a trend towards the inclusion of SPECT as an integral part of many recent prospective clinical studies, such as INSPIRE,[16] STICH[45] and COURAGE.[24 25] A randomised trial of rest SPECT imaging in the emergency room was able to demonstrate that a strategy of SPECT imaging was effective in reducing hospital admissions for chest pain without adverse outcomes when compared with standard care.[46] The results of these and similar studies will allow the practice of nuclear cardiology to be strengthened by a higher level of evidence.

NEW ADVANCES IN MOLECULAR IMAGING

The basis of conventional SPECT imaging is the Anger Camera, consisting of a large sodium iodide crystal coupled to multiple photomultiplier tubes. This technology was developed in the 1950s and has not fundamentally changed since then; all improvements in conventional SPECT imaging have been built on this platform, with its inherent limitations of resolution and sensitivity. These constraints have limited attempts to improve diagnostic accuracy. Lately, a number of vendors have now begun to design radically new cameras that make use of alternative geometries and cadmium zinc telluride (CZT) detectors that are much smaller and have inherently higher sensitivity and energy resolution than the conventional gamma camera detectors.[47] One such camera, the D-SPECT system, is already commercially in use and employs multiple rotating columns of CZT detectors that focus on the heart, resulting in SPECT studies that are completed in 2–4 min, substantially faster than the usual 15–20 min acquisitions on conventional system. Another vendor is also rolling out an ultrafast cardiac-dedicated camera utilising CZT detectors that will complete SPECT studies within 3–4 min. These new developments open new intriguing possibilities for nuclear cardiology. Higher sensitivity and resolution could potentially be used to improve patient throughput, image quality or reduce radiation dose, or to develop methods of quantifying cardiac perfusion more accurately.

At the same time, the success of PET-CT in clinical oncology and the availability of 16 and 64-slice PET-CT hybrid scanners have increased interest in cardiac PET and fusion of PET-CT studies.[48]

Nuclear cardiology is more than just myocardial perfusion imaging. There has been considerable research work in the development of tracers for ischaemic memory such as iodine-labelled B-methyl-*p*-(I-123)-iodophenyl-pentadecanoic acid which has potential in assessment of acute chest pain as well as episodic chest pain syndromes.[49] FDG is being explored as an agent to detect atherosclerotic lesions in arterial wall[50] and predict cardiac events. A range of imaging agents, such as F-18 lisinopril, is being explored to better understand the pathophysiology of heart failure.[51] Unlike the use of Tc-99m agents for MPI, these agents are not yet in widespread clinical use; some are at the stage of clinical testing, others are still exploratory, and many will remain research tools. It is too early to predict the impact of these developments. However, they remind us of the potential of molecular imaging in cardiology.

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