MOLECULAR IMAGING

Integration of coronary anatomy and myocardial perfusion imaging

Ron Blankstein and Marcelo F. Di Carli

Abstract | Advances in cardiovascular imaging have resulted in the development of multiple noninvasive techniques to evaluate myocardial perfusion and coronary anatomy, each of which has unique strengths and limitations. For example, CT angiography can directly visualize the presence of atherosclerosis, but the hemodynamic effect of many lesions identified by this technique is unknown. Alternatively, myocardial perfusion imaging enables a physiological assessment, but it may underestimate the extent of atherosclerosis in patients with multivessel disease. Dual-modality simultaneous imaging or multimodal sequential imaging techniques facilitate integration of information on both myocardial perfusion and coronary anatomy, and thus have the potential to improve diagnostic and prognostic evaluation, which could translate into improved care of patients. This Review discusses the strengths and limitations of the currently available individual noninvasive techniques for imaging coronary anatomy and myocardial perfusion. Approaches to integration of these imaging modalities are described, followed by an exploration of the clinical utility and future directions of hybrid imaging.

Blankstein, R. & Di Carli, M. F. *Nat. Rev. Cardiol*. **7**, 226–236 (2010); published online 9 March 2010; doi:10.1038/nrcardio.2010.15

Introduction

Despite many improvements in treatment and prevention, coronary artery disease (CAD) remains prevalent and represents a substantial health-care burden in industrialized and developing countries. Coronary heart disease is estimated to cause about one in every five deaths in the US and to result in an estimated total annual cost of US $165.4 billion.[1] The profound burden of this disease has led to the development of new therapies and noninvasive detection techniques. Imaging developments have focused on anatomical evaluation of the coronary arteries and physiological assessments of myocardial perfusion (Figure 1). While remarkable progress has been made in both approaches, intense debate is ongoing about the strengths and weaknesses of the various technologies and the appropriateness of their clinical use. Furthermore, the development of PET–CT and SPECT–CT techniques, which combine nuclear imaging and multidetector CT devices, has led to renewed interest in the development of approaches to integrate anatomical and perfusion imaging.

The many advances in anatomical and myocardial perfusion imaging, as well as the growth of hybrid imaging techniques that use different modalities to acquire data in the same setting, make a review of these developments and a discussion as to their potential complementary use particularly timely. This Review, therefore, aims to inform clinicians and researchers about technological developments to explore the advantages and disadvantages of the different, currently available individual techniques and discuss the rationale for integrating these techniques. Finally, we discuss potential

MedscapeCME® Continuing Medical Education online

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medscape, LLC and Nature Publishing Group. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

Medscape, LLC designates this educational activity for a maximum of 1.0 **AMA PRA Category 1 Credits™**. Physicians should only claim credit commensurate with the extent of their participation in the activity. All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test and/or complete the evaluation at http://www.medscapecme.com/journal/nrcardio; and (4) view/print certificate.

Learning objectives

Upon completion of this activity, participants should be able to:

1. Describe implications of coronary artery calcium scores for long-term risk for myocardial ischemia.
2. Describe the accuracy of coronary computed tomographic (CT) angiography in predicting coronary artery disease.
3. Describe the pros and cons of myocardial perfusion imaging.
4. Describe the advantage of positron emission tomography (PET)-CT over other perfusion tests.
5. Identify the limitations of cardiac magnetic resonance imaging (MRI) for assessing coronary risk factors.

Noninvasive Cardiovascular Imaging Program, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA (**R. Blankstein, M. F. Di Carli**).

Correspondence to:
M. F. Di Carli
mdicarli@partners.org

Competing interests
The authors and the Journal Editor B. Mearns declare no competing interests. The CME questions author D. Lie has served as a nonproduct speaker for "Topics in Health" for Merck Speaker Services.

clinical applications of hybrid imaging as well as future directions of such approaches.

Anatomical imaging techniques

Assessment of coronary artery calcium

Non-contrast-enhanced, electrocardiographically gated scanning for coronary artery calcium (CAC) offers a reproducible, inexpensive, and easy-to-perform method of reliably determining whether coronary calcification is present or absent. When present, the extent of calcification can be quantified by validated scoring techniques (a score of 0 means no calcification and minimal risk of a cardiovascular event in the next 5 years, a score of ≥100 equates to medium calcification and risk, while a score of ≥400 indicates severe calcification and increased risk),[2] which reflect the burden of atherosclerosis in coronary arteries. Patients require no preparation and the examination can be performed with most types of stand-alone CT scanners as well as hybrid SPECT–CT and PET–CT platforms. With appropriate techniques, the radiation dose associated with CAC scanning is minimal (~1–2 mSv), which makes this test a low-risk option.[3]

CAC scores provide useful prognostic data.[4] The Multi-Ethnic Study of Atherosclerosis (MESA) involved 6,722 individuals with no known cardiovascular disease (median follow-up ~4 years). In comparison to participants without calcification (CAC score 0), those with a score >300 had a nearly sevenfold higher adjusted risk of a major coronary event.[5] Importantly, the presence of coronary calcification provided predictive information beyond that derived from the Framingham risk score. In a meta-analysis conducted by Sarwar *et al.*, a CAC score of 0 was associated with an excellent long-term prognosis: cardiovascular event rates were 0.56% for asymptomatic and 1.80% for symptomatic patients, respectively, during follow-up (mean 51 months).[6] A point worthy of note is that the literature supporting use of CAC scores is primarily based on screening populations. The use of CAC score alone as a diagnostic tool in symptomatic patients has not been advocated, as it is not specific for the diagnosis of obstructive CAD[7] and, in younger patients, may miss the presence of exclusively noncalcified plaques.[8]

Despite the powerful prognostic data afforded by CAC scores, evidence that the use of such imaging biomarkers leads to improved outcomes is limited.[9] This lack of substantiation is related to the fact that studies addressing this question would be complex, unethical (they would require random allocation of patients with elevated CAC scores to less aggressive therapy, or even to no treatment), and would require a long follow-up period. Nevertheless, the literature suggests that identification of coronary atherosclerosis by CAC scanning does lead to lifestyle changes and the intensification of medical therapies.[10–12]

Key points

- Cardiac CT can directly visualize the presence of atherosclerosis and, if images are of sufficient quality, determine whether obstructive anatomical stenosis is present
- Cardiac CT is an excellent technique for excluding obstructive coronary artery disease, but has a limited capacity to identify the presence of ischemia
- Each of the techniques used for myocardial perfusion imaging has specific strengths and limitations, but PET is currently considered to be the most robust method for identifying and quantifying ischemia
- The combination of coronary imaging and myocardial perfusion imaging offers many advantages, including the potential to improve diagnosis and predictions of prognosis
- Although use of hybrid imaging techniques may improve therapeutic decision-making, issues relating to selection of patients, radiation exposure, and cost-effectiveness remain to be addressed
- Rapid technical advances will further improve multimodality imaging and will pave the way for targeted molecular imaging

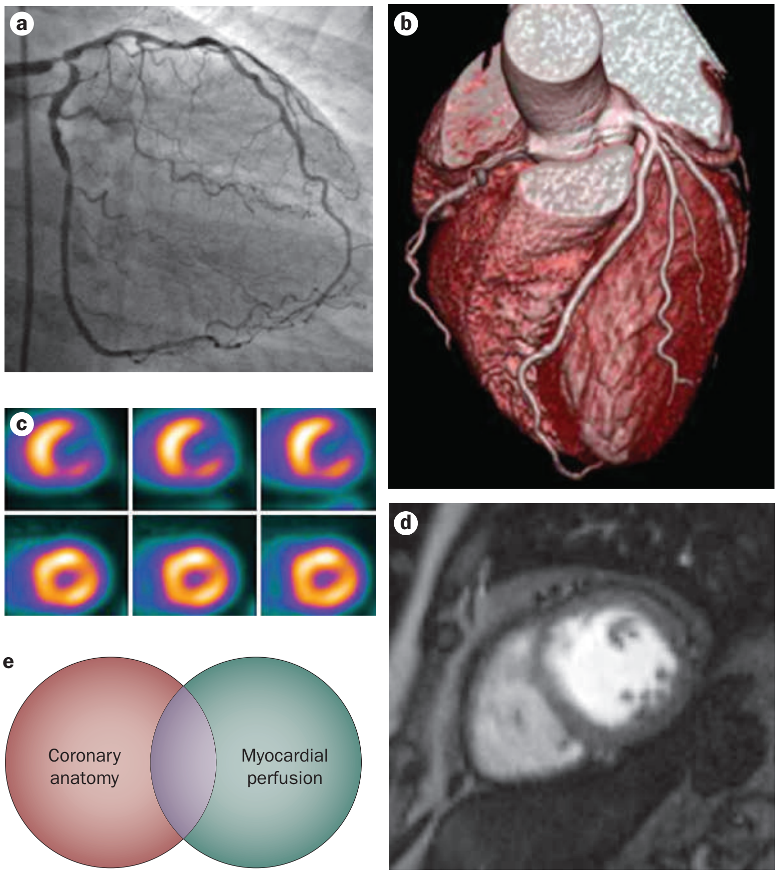

Figure 1 | Examples of images obtained by techniques used to assess coronary anatomy and myocardial perfusion. Anatomical assessment is possible with **a** | coronary angiography and **b** | CT angiography. Myocardial perfusion imaging can be performed with **c** | SPECT and/or PET and **d** | cardiac MRI. **e** | The Venn diagram illustrates that coronary anatomy and myocardial perfusion imaging predominantly provide unique information. The data provided by these techniques do overlap to a small extent, but combinations of imaging modalities have the potential to offer complementary information. Abbreviation: SPECT, single-photon emission CT.

CT angiography

Within the past 10 years, advances in technology have enabled contrast-enhanced, electrocardiographically gated coronary CT angiography to visualize both calcified and noncalcified plaques, as well as to estimate the severity of any stenosis present (Figure 2). During the procedure, intravenous contrast is administered and image

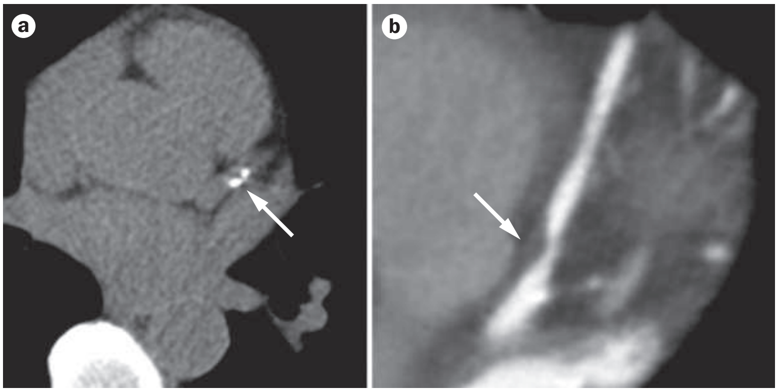

Figure 2 | Images obtained by cardiac CT. **a** | A coronary artery calcium scan from a 45-year-old man with a family history of premature coronary heart disease. In this noncontrast CT scan with electrocardiographic gating, the arrow points to the presence of calcified plaque in the proximal LAD. **b** | Coronary CT angiography in a 48-year-old woman with chest pain on exertion. In this contrast-enhanced scan with electrocardiographic gating, the arrow points to a large, noncalcified plaque in the proximal LAD. Abbreviation: LAD, left anterior descending coronary artery.

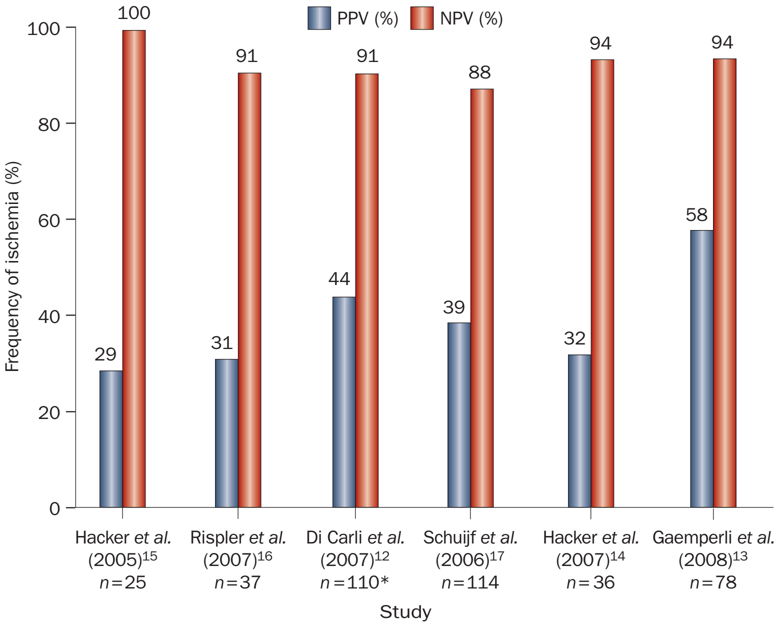

Figure 3 | Frequency of ischemia in vessels with ≥50% stenosis by CT angiography. All patients in each of the six studies shown underwent both perfusion imaging (SPECT or *PET) as well as CT angiography. Abbreviations: NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission CT.

acquisition is carefully timed to occur while contrast opacifies the coronary arteries. The best-quality images of the coronary arteries that can currently be obtained have a spatial resolution of ~0.6 mm and a temporal resolution of 83–175 ms. To reduce motion-related artifacts, β-blockers are administered to achieve a heart rate of about 60 bpm. The resulting high-resolution, three-dimensional data sets permit visualization of the coronary arteries in any plane.

Coronary CT angiography cannot be used in all patients. This modality is contraindicated in patients with renal dysfunction or who have allergies to intravenous iodinated contrast. In patients with elevated heart rates or when excessive motion is present during scanning, poor image quality often limits the usefulness of this technique.[13] In elderly patients or those with multiple cardiovascular risk factors, extensive calcifications can lead to calcium blooming artifacts. In such cases, areas of calcification appear larger than their actual size and can result in false-positive findings (that is, overestimation of the presence of obstructive CAD) or to coronary artery segments being nonevaluable. When anatomical obstructive disease is identified by CT angiography, the functional relevance of many lesions cannot be assessed in terms of the ischemic burden. Stenosis of ≥50% on CT angiography has a low positive predictive value (29–58%) for predicting myocardial ischemia on SPECT or PET (Figure 3).[14–19] Although using a higher threshold (namely ≥70% instead of ≥50% stenosis) would probably improve the positive predictive value with regard to predicting myocardial ischemia, many lesions that show only moderate stenosis on CT angiography can be clinically challenging to manage.

Data on the accuracy of CT angiography for detection of coronary artery stenosis relative to that of invasive angiography have been reported in three multicenter studies (Table 1).[20–22] On a per-patient basis, the average sensitivity and specificity, weighted by number of patients, of CT angiography for detecting at least one coronary artery with ≥50% stenosis were 93% and 78%, respectively. The corresponding weighted average positive predictive and negative predictive values were 82% and 93%, respectively. In one study, however, specificity was reduced from 87% to 53% among patients with high calcium scores (>400).[20] An important caveat is that the diagnostic accuracy of CT angiography reported in these trials refers only to disease in vessels of ≥1.5 mm diameter.

The high negative predictive value of CT angiography means that a normal scan result effectively excludes obstructive CAD and abolishes the need for further investigation. The limited capability of this technique to determine the severity of stenosis and to predict ischemia can make abnormal scan results difficult to interpret, however, especially in terms of determining whether a need exists for invasive angiography or coronary revascularization.[23–25]

Myocardial perfusion imaging

A considerable body of evidence supports the use of myocardial perfusion imaging to identify obstructive CAD, quantify the amount of myocardium at risk, assess the extent of viable tissue, and guide patients' management with regard to the need for revascularization or aggressive medical therapies. Myocardial perfusion imaging is typically accomplished by SPECT or PET, but cardiac MRI and CT have also been used to visualize myocardial perfusion under stress and at rest.[26] Despite widespread use and acceptance of the former two techniques for assessing perfusion, however, they generally only reveal ischemia in myocardial territories supplied by the most severely stenosed vessels. Another drawback of myocardial perfusion imaging is that it cannot

Table 1 | Multicenter trials that compared CT angiography with invasive angiography in the detection of ≥50% stenosis

Study (year)	Patients	Centers	CAC score exclusion threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Prevalence (%)
Per-patient analysis								
ACCURACY (2008)[18]	230	16	None	95	83	64	99	25
Meijboom *et al.* (2008)[19]	360	3	None	99	64	86	97	68
CORE64 (2008)[20]	291	9	<600	85	90	91	83	56
Average (weighted by number of patients)	NA	NA	NA	93	78	82	93	53
Per-vessel analysis								
ACCURACY (2008)[18]	910	16	None	84	90	51	99	10
Meijboom *et al.* (2008)[19]	1,440	3	None	95	77	59	98	26
CORE64 (2008)[20]	886	9	<600	75	93	82	89	31
Average (weighted by number of vessels)	NA	NA	NA	86	85	63	96	23

Abbreviations: CAC, coronary artery calcification; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

detect or quantify subclinical atherosclerosis.[14,19] This limitation is not unexpected, since myocardial perfusion imaging methods are optimized for identification of flow-limiting stenoses.

SPECT

SPECT is the most frequently performed myocardial perfusion imaging procedure in the US. An intravenously injected, radiolabeled tracer is taken up from the blood by viable myocytes in proportion to regional myocardial perfusion. Detection of the tracer enables tomographic images of myocardial perfusion to be obtained that show areas of normal and abnormal tissue perfusion.

The mean sensitivity for detection of ≥50% angiographic stenosis achieved with SPECT is 87% (range 71–97%) and the specificity is 73% (range 36–100%).[27] This specificity value is low due to the known effects of verification bias,[28] whereby a study that only included patients who underwent post-test catheterization would have decreased numbers of true and false negatives.[29] Moreover, if not properly recognized, attenuation artifacts (typically from breast tissue or the diaphragm) can lead to equivocal or false-positive findings. The use of attenuation correction methods and analysis of wall motion from gated studies reduces the rate of false-positive results and improves the specificity of the test.[27] Rarely, false-negative findings can result from a global or balanced reduction in myocardial perfusion, typically in patients with extensive, obstructive CAD.

Robust data support the prognostic value of SPECT myocardial perfusion imaging.[30–33] The basic premise underlying use of this technique for prognostic assessments is that clinical risk increases with myocardial abnormality size, which reflects the extent of obstructive CAD, and severity, which reflects the hemodynamic effect of underlying coronary stenoses. Specifically, patients with no history of CAD who have normal myocardial perfusion imaging findings during exercise generally have a low annual event rate (<0.7% for cardiac death or nonfatal myocardial infarction).[27] The clinical risk of cardiac events increases in a linear fashion with increasing magnitudes of perfusion abnormality.[27] Risk is further raised in patients with diabetes or chronic kidney disease.[34–36] The results of myocardial perfusion imaging represent a clinically relevant and cost-effective approach to guiding patients' management, as individuals who have moderate to severe myocardial ischemia on SPECT are likely to benefit from coronary revascularization.[37,38]

Compared with invasive angiography, SPECT is a relatively insensitive technique that cannot accurately delineate the extent of obstructive CAD, especially in patients with multivessel disease. For example, Berman *et al.*[39] reported that SPECT identified high-risk disease with moderate to severe perfusion defects (>10% of the myocardium on quantitative analysis) in only 59% of 101 patients who had ≥50% angiographic stenosis of the left main coronary artery. Conversely, 15% of these patients showed no substantial perfusion defects (>5% of the myocardium).[39]

PET

PET is often considered the gold standard for noninvasive assessment of myocardial perfusion and viability.[40] Although the adoption of PET has been hampered by the limited availability of devices and complex issues related to the production and delivery of radiopharmaceuticals, the FDA approval of PET radiolabeled tracers in 1995 and 2003 led to commercial marketing of agents based on ^{82}Rb and ^{18}F-fluorodeoxyglucose. These developments, together with technological advances, have made clinical application of this technology possible in large-volume clinical centers.[40,41]

PET has many advantages over SPECT, including improved spatial and temporal resolution and a robust, quantitative nature that allows for measurement of absolute myocardial blood flow (in ml·min^{-1}/g). In addition, reliable attenuation correction improves the specificity of the technique, because it reduces the number of artifacts leading to false-positive perfusion defects.[42] Another noteworthy consideration is that radiation exposure is

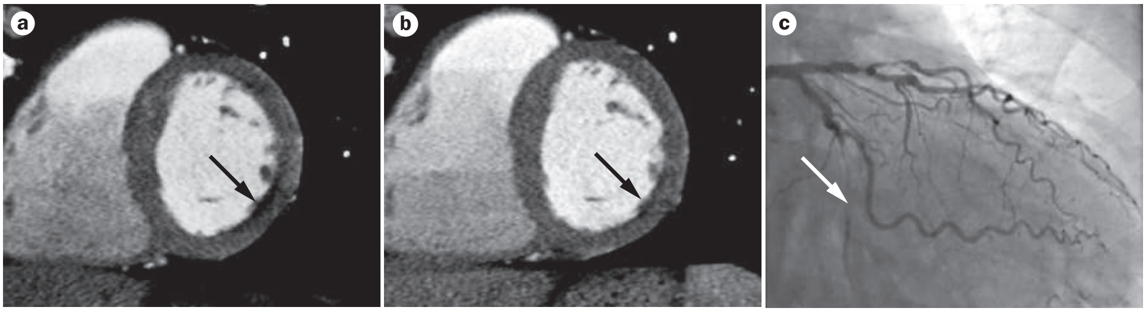

Figure 4 | CT myocardial perfusion images. The patient was a 63-year-old man with a history of hypertension and dyslipidemia who had experienced a syncopal episode. **a** | A contrast-enhanced image obtained during adenosine infusion revealed a perfusion defect (arrow) in the basal inferolateral wall. **b** | During a separate contrast-enhanced scan taken at rest, the subendocardial perfusion defect in the same territory (arrow) was minimal, which suggested that the defect was mostly reversible. **c** | Invasive angiography revealed a subtotal occlusion of the distal left circumflex artery (arrow) after the first diagonal branch.

generally lower with PET than with SPECT,[43] owing to the short half-life of the radiolabeled tracers. The reported average sensitivity of PET perfusion imaging for detecting angiographic stenosis of ≥50% is 91% (range 83–100%) and the specificity is 89% (range 73–100%).[44] Similarly to myocardial perfusion imaging performed with SPECT, PET-based imaging has incremental value for predicting future cardiovascular events and death; increasing percentages of ischemia on PET myocardial perfusion imaging are associated with increased risk.[45–47]

Since functional assessment can be performed during peak vasodilator-induced (or dobutamine-induced) stress, the patient's left ventricular ejection fraction (LVEF) reserve can be quantified and used to exclude the presence of high-grade multivessel disease (that is, multivessel or left main coronary artery stenosis).[48] PET, however, has lower sensitivity for the detection of multivessel disease than does invasive imaging.[48] Two quantitative approaches may help to mitigate this limitation. First, PET enables quantification of peak stress left ventricular function.[48] In patients without severe disease, LVEF increases during peak stress, whereas in those with obstructive CAD, it drops even in the absence of apparent perfusion defects. The size of the decrease is inversely related to the extent of obstructive CAD. Accordingly, incorporating information on the change in LVEF from baseline to peak stress improves the sensitivity of PET from 50% to 79% for correctly ascertaining the presence of multivessel disease.[48]

Second, PET can measure absolute myocardial blood flow and, in turn, coronary vasodilator reserve. In patients with balanced ischemia or diffuse CAD, assessment of this latter feature might reveal coronary disease that could otherwise be missed if only a relative assessment of myocardial perfusion is performed.[49]

Cardiac MRI

Cardiac MRI can be used to assess myocardial perfusion during an injection of gadolinium contrast. Qualitative or quantitative analysis of rapidly acquired, sequential images (a 'cine loop') obtained during the first pass of contrast into the myocardium can identify perfusion defects present at rest or under pharmacologically induced vasodilatation. An advantage of cardiac MRI is that other valuable information can be obtained during the scan: late-enhancement imaging can identify areas of prior myocardial infarction, scar tissue, or infiltration, and cine imaging can be used to quantify right and left ventricular size and function. Other advantages of cardiac MRI include high spatial resolution—typically 1–3 mm—and no exposure to ionizing radiation. This imaging modality cannot, however, be used in patients who are claustrophobic or who have implanted ferromagnetic objects, such as pacemakers, defibrillators and metallic clips. Moreover, administration of gadolinium is contraindicated in patients with a creatinine clearance rate ≤30 ml/min/1.73 m^2 to prevent the rare but devastating complication of nephrogenic systemic fibrosis.[50] The complexity of cardiac MRI limits its use to centers that possess technical expertise and have the necessary equipment.

Stress perfusion cardiac MRI has very good diagnostic accuracy for detecting anatomical stenosis. A meta-analysis of pooled data from 14 studies that involved 1,516 patients who underwent stress perfusion imaging concluded that this technique had a per-patient sensitivity of 91% and specificity of 81% for the detection of ≥50% stenosis.[51] The prevalence of disease in this population was 57.4%; further studies are, therefore, needed to assess the accuracy of this modality in patients at low risk of disease. The multicenter MRI for Myocardial Perfusion Assessment in Coronary Artery Disease Trial (MR-IMPACT)[52] showed similar diagnostic accuracy for stress perfusion MRI and SPECT imaging in direct comparison with invasive coronary angiography. This study has several noteworthy limitations. Gated SPECT was not available for approximately half of the patients. The MRI technique used was also inconsistent, as patients were randomly allocated one of five different doses of gadolinium. When the patients who underwent perfusion cardiac MRI with the optimal gadolinium dose of 0.1 mmol/kg ($n = 42$) were compared with the entire SPECT population ($n = 212$), the receiver operator characteristic analysis demonstrated a trend towards better performance for perfusion cardiac MRI (areas under the curve of 0.86 ± 0.06 for MRI versus 0.67 ± 0.05 for

Table 2 | The prevalence of clinically important CAC in patients with normal myocardial perfusion imaging findings

Study	Number of patients	Average age (years)	Population studied (patients with CAD)	MPI findings		Prevalence of calcification in individuals with negative MPI findings	
				Negative	Positive	CAC score ≥0 (%)	CAC score ≥400 (%)
He *et al.* (2000)[62]	411	58	87% asymptomatic*	330	81	NR	22
Berman *et al.* (2004)[61]	1,195	58	51% asymptomatic*	1,119	76	98	31
Schenker *et al.* (2008)[63]	621	61	Intermediate risk, referred for PET	442	179	99	47
Uebleis *et al.* (2009)[64]	260	60	Stable CAD	165	95	NR	34
Total	2,487	NA	NA	2,056	431	NA	33‡

Only studies that involved more than 100 patients and included data on CAC scores >400 in patients with negative MPI findings are listed. *Risk level not specified. ‡Weighted average. Abbreviations: CAC, coronary artery calcification; CAD, coronary artery disease; MPI, myocardial perfusion imaging; NA, not applicable; NR, not reported; NPV, negative predictive value; PPV, positive predictive value.

SPECT, $P = 0.013$). Although Schwitter *et al.*[52] suggested that some comparisons demonstrated a trend towards the superiority of cardiac MRI over SPECT, further studies that compare contemporary techniques are needed.

A current potential limitation of cardiac MRI perfusion assessments, which is unique to this modality, is that images may show false-positive defects related to transient dark rim artifacts in the subendocardium. Such artifacts may limit the specificity of cardiac MRI in relation to detection of small perfusion defects. These artifacts were thought to be caused by so-called Gibbs ringing at the blood–myocardial interface, magnetic susceptibility due to the rapid bolus injection of gadolinium, banding movement artifacts, and partial volume effects between the left-ventricular blood pool and the myocardium.[53] However, an experienced reader can often differentiate between a dark rim artifact and a real perfusion defect, as a true myocardial perfusion defect tends to have a constant appearance and remains visible for an extended duration.

CT

Preliminary studies indicate that contrast-enhanced CT might be useful to visualize myocardial perfusion. As with stress perfusion MRI, this technique is based on acquiring CT images during the first pass of iodinated contrast into the myocardium. When the myocardium is visualized appropriately, areas of hypoenhancement correspond to perfusion defects. When seen under resting conditions, such defects represent areas of prior myocardial infarction, particularly if they are also associated with wall thinning or intramyocardial calcification.[54] By contrast, when CT images are acquired during administration of vasodilators, such as adenosine, areas of inducible ischemia can be visualized (Figure 4).[55,56] Limitations of this technique include motion-related and beam-hardening artifacts that can mimic areas of myocardial hypoenhancement.

While the technique remains experimental, the prospect of being able to perform a single scan that combines the anatomical information provided by CT angiography with assessment of CT myocardial perfusion during pharmacologic stress is intriguing.[26,57] Analogous to MRI techniques, an electrocardiographically gated CT scan acquired 6–10 min after the administration of iodinated contrast (late-enhancement CT) can be used to visualize myocardial scar.[58] CT-based perfusion imaging has been reviewed in detail elsewhere.[59]

Integrated imaging techniques

Rationale for an integrated approach

Clearly, each imaging technique has unique advantages. High-resolution imaging of cardiac and coronary anatomy with CT can identify subclinical coronary atherosclerosis, while perfusion imaging can identify abnormalities in myocardial blood flow or metabolism. The integration of data derived by these complementary techniques may thus offer improved diagnostic and prognostic information.[60–62] The currently available modalities can be combined in several different ways.

CT with calcium scoring

While perfusion imaging is well suited to detection of obstructive atherosclerosis, it is not sensitive enough to detect subclinical disease; thus, the addition of CAC scoring can improve patients' risk stratification. This issue may be particularly important for patients with normal perfusion findings, in whom the detection of subclinical atherosclerosis might result in a more precise risk assessment than would otherwise be possible; approximately one-third of patients who have normal findings on SPECT or PET myocardial perfusion imaging have a CAC score >400 (Table 2).[63–66] In otherwise intermediate-risk patients, a CAC score ≥400 is considered a coronary heart disease risk-equivalent; consequently, intermediate-risk patients with a CAC score above this threshold should be reclassified as being at high risk and considered for further therapies.[7]

Even among patients with perfusion abnormalities on SPECT or PET, the CAC score can improve risk stratification. In 621 patients who underwent stress PET perfusion imaging and CAC scoring,[65] a comparison of risk-adjusted outcomes demonstrated that, for individuals with any degree of perfusion abnormality, a stepwise increase in adverse events (death and myocardial infarction) occurred with increasing CAC scores.

Box 1 | Approaches to integration of multiple imaging modalities

Simultaneous dual-modality acquisition
Two imaging modalities (SPECT or PET ± CT) are integrated into one platform to allow both data types to be collected during a single imaging session. CT is used for attenuation correction and can also be used in CT angiography, CAC, or both.

Sequential multimodal acquisition
Sequential image acquisition using multiple modalities enables an initial assessment with one modality.

- CT angiography (with or without CAC) may be a reasonable first test in low-risk populations, followed by SPECT or PET if plaque of uncertain physiological importance is identified.
- SPECT or PET could be used as the initial test in high-risk populations, followed by either CT angiography (if myocardial perfusion findings are equivocal or abnormal) or CAC (if further risk assessment is needed).

Abbreviations: CAC, coronary artery calcium scanning; SPECT, single-photon emission CT.

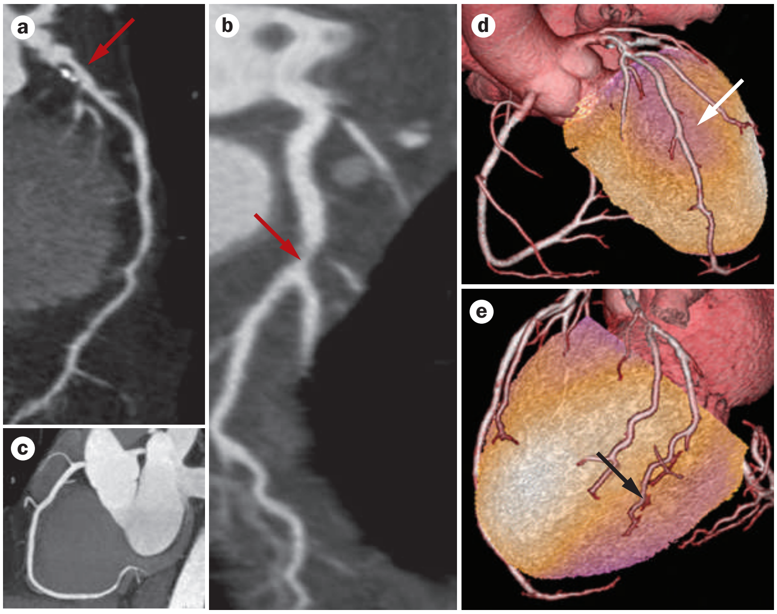

Figure 5 | PET and CT hybrid images obtained from a 60-year-old man with diabetes and hypertension undergoing investigation for chest pain. **a** | Coronary CT angiography demonstrated a mixed plaque in the proximal LAD (arrow) that resulted in moderate to severe stenosis. **b** | A substantial noncalcified plaque is shown in the mid LCx (arrow). **c** | The RCA was free of disease. ^{82}Rb PET perfusion images obtained during regadenoson administration were combined with volume-rendered CT images. **d** | The hybrid images reveal a perfusion defect in the basal and mid anterior wall, a myocardial territory directly supplied by the LAD (white arrow). **e** | In addition, a perfusion defect is also seen along the inferolateral wall, a myocardial distribution directly supplied by the distal LCx and/or obtuse marginal artery (black arrow). Abbreviations: LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; RCA, right coronary artery.

Simultaneous dual-modality imaging

Technologies

The introduction of SPECT–CT and PET–CT machines enabled data to be acquired from both modalities in a single session (Box 1). In 1992, the first prototype to integrate CT and PET within the same device enabled CT images to be used for attenuation correction.[67] Over the next few years, the advantages offered by such devices became increasingly clear, and today five different vendors offer PET–CT machines. Such an approach has many potential advantages but also introduces new challenges. Contemporary dual-modality (PET–CT and SPECT–CT) scanners utilize CT images for attenuation correction, which increases diagnostic certainty and reduces the number of equivocal findings.[68,69] However, attenuation correction remains a notable challenge in cardiac imaging,[70] and artifacts remain in 30–60% of SPECT–CT and PET–CT images.[70,71] These artifacts are usually related to misalignment of the SPECT or PET (emission) and CT (transmission) data sets, caused by the patient's movements and cardiac or respiratory motion.[70,72] Such errors may lead to regional defects and, frequently, heterogeneity in quantitative tracer distribution.[73] Appropriate quality control and use of registration software is, therefore, crucial in the interpretation of SPECT–CT and PET–CT images.

Selection of patients

One of the most compelling reasons for use of integrated imaging is its potential for improving decision-making in management of patients. In an era of rapidly escalating health-care costs, however, tests can only be justified if the results are capable of improving treatment outcomes. In addition, clinical risks and benefits must be taken into account. Although use of some imaging modalities might increase confidence in ruling out CAD, the risks associated with radiation exposure prohibit their widespread use.[74] Innovations in CT have, however, led to dramatically reduced radiation exposure.[75–79] For selected populations of patients, the overall clinical value might, therefore, outweigh the risks. A noteworthy point is that the key to effective use of integrated imaging technologies is to identify which patients will benefit from such combined approaches, as well as to understand which individuals do not require such testing.

The need for and choice of dual-modality imaging is likely to be highly dependent on the individual patient's level of risk as well as the clinical question at hand. For instance, the majority of symptomatic, low-risk patients probably do not require dual-modality imaging. By contrast, symptomatic patients at intermediate to high risk of obstructive CAD might benefit from a dual-modality approach, whereby the extent (and, less reliably, the severity) of coronary atherosclerosis can be demonstrated by CT angiography whereas the amount of ischemia—and thus the need for coronary revascularizion—can be identified by myocardial perfusion imaging. In patients with multivessel disease, the integration of both modalities could then help to determine which specific anatomical lesions are associated with ischemia and should be selectively targeted for revascularization. When fixed perfusion defects are identified in the absence of substantial ischemia, metabolic imaging with ^{18}F-fluorodeoxyglucose PET could be used to assess the extent of viable myocardium and determine whether the patient would benefit from coronary revascularization. In very-high-risk, symptomatic patients, CAC scoring and CT angiography are unlikely to provide useful diagnostic or prognostic information and proceeding directly to myocardial perfusion imaging or (in some cases) directly to invasive angiography is reasonable.

Sequential multimodal imaging

An alternative approach to integration involves the sequential acquisition of perfusion and anatomical data (Box 1). One test is performed and completed, and the information collected dictates the need for and choice of the subsequent method. An advantage of this approach is that not all patients will require additional imaging studies, which could reduce overall costs. For example, in patients at low to intermediate risk, if CT angiography is performed first and has negative findings, the high negative predictive value of this imaging modality for excluding ischemia[14–19] indicates that perfusion imaging is unlikely to be of use. Alternatively, patients with equivocal SPECT findings might then undergo CT angiography to clarify whether obstructive coronary disease is present or absent,[80] or might undergo CAC scoring to identify whether atherosclerosis is present. A disadvantage, however, is that each scan requires interpretation before further recommendations can be made, which (depending on the specific examination interpretation workflow followed) could result in a time delay to diagnosis.

Myocardial perfusion and CT angiography

Combining the complementary information of coronary anatomy and myocardial perfusion imaging seems advantageous, as the weaknesses of each modality can be offset by the strengths of the other. CT angiography cannot provide functional data and is unable to detect obstructive disease in calcified or very small vessels; however, these challenges are easily met by myocardial perfusion imaging. Similarly, the limitations of myocardial perfusion imaging, namely a limited capability to detect the presence of subclinical atherosclerosis and a tendency to underestimate the extent of atherosclerosis, could be partially offset by anatomical imaging.

Several studies support the notion that dual-modality imaging offers superior diagnostic information.[18,81,82] In a cohort of 56 symptomatic patients, Rispler *et al.*[18] reported that use of SPECT–CT angiography (versus CT angiography alone) significantly improved the accuracy of diagnosing obstructive CAD. The dual-modality approach had better specificity than CT alone (95% versus 63%) and a higher positive predictive value (77% versus 31%), but equivalent sensitivity and negative predictive value.[18] Combining data on anatomical stenosis and myocardial perfusion also seems to result in an incremental improvement in the prediction of adverse cardiovascular events.[62]

Hybrid images

Over the past 10 years, experience from the field of oncology has highlighted the superiority of using multimodal techniques to create hybrid (merged) images for detection and staging of cancer. This concept has been applied to the evaluation of cardiovascular disease, but experience with such merged images of the heart (Figure 5) thus far is limited.

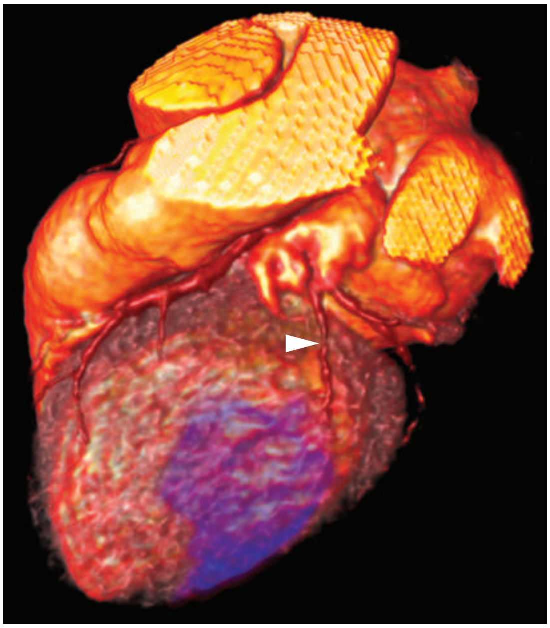

Figure 6 | CT and MRI hybrid image. The purple area shows an adenosine-induced stress perfusion defect along the anterolateral wall that corresponds with a high-grade stenosis of the first diagonal coronary artery (arrowhead). The hybrid image displayed incorporates perfusion data from cardiac MRI overlaid onto volume-rendered data obtained from cardiac CT. Permission obtained from Dr Hatem Alkadhi, Institute of Diagnostic Radiology, University Hospital Zurich, Zurich, Switzerland.

In a study by Santana and colleagues,[74] 50 patients underwent myocardial perfusion imaging (SPECT or PET) and CT angiography. Hybrid images provided incremental diagnostic value for detecting obstructive CAD confirmed on invasive angiography, compared with those obtained by myocardial perfusion imaging alone or separate images obtained by each technique viewed side by side. The incremental value of hybrid imaging seemed to be limited to patients with multivessel disease; in this subgroup, sensitivity increased by 17% when this technique was used.[74]

Hybrid images do not require data sets to be acquired on the same scanner or even in the same location. Currently, several software products enable the fusion of data sets; for example, stand-alone SPECT or PET images can simply be overlaid on cardiac CT scans.[61] Although such ease of fusion facilitates the interpretation of information,[83] integration of some forms of myocardial perfusion imaging and coronary anatomy, such as fusion of CT angiography and perfusion MRI (Figure 6) may present different technical challenges.

Future directions

Technological advances

Imaging techniques continue to develop across all modalities. New generations of CT scanners are offering improved *z*-axis coverage,[84] increased gantry rotation speeds, which improve temporal resolution, and improved detectors,[85] which increase spatial resolution.

Developments in iterative reconstruction algorithms have the potential to improve image quality and possibly lead to a decrease in tube current required, which would further reduce patients' radiation exposure. In the field of nuclear imaging, advances in PET and increased availability of radiolabeled tracers are expected to broaden adoption of this modality.[40] At the same time, hardware innovations in SPECT have led to new, small-footprint imaging systems that offer improved spatial resolution as well as increased comfort for patients.[86]

Molecular imaging

A future application of hybrid imaging relates to the ability of CT or MRI to provide an anatomical 'road map' to show the location of molecularly targeted imaging agents. In cardiovascular imaging, such dual-modality imaging approaches could be especially useful in patients with atherosclerosis. For example, CT could help to delineate plaques and, with use of a targeted imaging probe, reveal the location of inflammation in relation to those plaques.[87] In addition to identifying metabolic abnormalities, such as the presence of inflammation, this approach may be used to visualize specific molecular targets and pathways that underlie pathophysiological changes. For example, molecular imaging techniques could ultimately provide a reliable means of identifying vulnerable plaque, and thus aid the selection of patients who might benefit from future, highly selective, potent therapies.[88] In turn, findings from hybrid imaging can be used to predict adverse outcomes or perhaps to estimate the likelihood of response to targeted therapies. The proposed integration of PET and MRI might further expand the possibilities for combining anatomical and functional data while localizing molecular targets.[89,90]

Conclusions

The integration of coronary anatomy and myocardial perfusion data enables dual-modality imaging approaches to detect and quantify anatomical features of CAD and to determine their physiological relevance. In turn, this information may improve risk assessment, diagnosis and management of patients with CAD. In the future, hybrid images that combine detailed anatomical information obtained from CT or MRI with high-sensitivity detection of radiolabeled agents targeted to specific pathways may have a central role in molecular diagnosis and therapy. Many of these technological developments are exciting; however, important challenges such as cost-effectiveness and radiation exposure will be important to address. Emphasis should be placed on identifying which populations of patients will derive the greatest benefit from dual-modality techniques.

Review criteria

This article is based on a comprehensive review of English-language papers published after 1990 in the PubMed database. Search terms included "myocardial perfusion imaging", "single photon emission computed tomography", "positron emission tomography", "coronary artery calcium scoring", "computed tomography", "coronary angiography", "magnetic resonance imaging", "hybrid imaging", "integrated imaging", and "diagnostic accuracy". The reference lists of the articles identified during this search were checked for additional publications.

1. Lloyd-Jones, D. *et al.* Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* **119**, 480–486 (2009).
2. Agatston, A. S. *et al.* Quantification of coronary artery calcium using ultrafast computed tomography. *J. Am. Coll. Cardiol.* **15**, 827–832 (1990).
3. Gerber, T. C. *et al.* Ionizing radiation in cardiac imaging: a science advisory from the American Heart Association Committee on Cardiac Imaging of the Council on Clinical Cardiology and Committee on Cardiovascular Imaging and Intervention of the Council on Cardiovascular Radiology and Intervention. *Circulation* **119**, 1056–1065 (2009).
4. Alexopoulos, N. & Raggi, P. Calcification in atherosclerosis. *Nat. Rev. Cardiol.* **6**, 681–688 (2009).
5. Detrano, R. *et al.* Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N. Engl. J. Med.* **358**, 1336–1345 (2008).
6. Sarwar, A. *et al.* Diagnostic and prognostic value of absence of coronary artery calcification. *JACC Cardiovasc. Imaging* **2**, 675–688 (2009).
7. Greenland, P. *et al.* ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). *J. Am. Coll. Cardiol.* **49**, 378–402 (2007).
8. Rosen, B. D. *et al.* Relationship between baseline coronary calcium score and demonstration of coronary artery stenoses during follow-up. MESA Multi-Ethic Study of Atherosclerosis. *JACC Cardiovasc. Imaging* **2**, 1175–1183 (2009).
9. Arad, Y., Spadaro, L. A., Roth, M., Newstein, D. & Guerci, A. D. Treatment of asymptomatic adults with elevated coronary calcium scores with atorvastatin, vitamin C, and vitamin E: the St Francis Heart Study randomized clinical trial. *J. Am. Coll. Cardiol*. **46**, 166–172 (2005).
10. Taylor, A. J. *et al.* Community-based provision of statin and aspirin after the detection of coronary artery calcium within a community-based screening cohort. *J. Am. Coll. Cardiol.* **51**, 1337–1341 (2008).
11. Wong, N. D. *et al.* Does coronary artery screening by electron beam computed tomography motivate potentially beneficial lifestyle behaviors? *Am. J. Cardiol.* **78**, 1220–1223 (1996).
12. Thompson, R. C. *et al.* Clinical utility of coronary calcium scoring after nonischemic myocardial perfusion imaging. *J. Nucl. Cardiol.* **12**, 392–400 (2005).
13. Bamberg, F. *et al.* Predictors of image quality of coronary computed tomography in the acute care setting of patients with chest pain. *Eur. J. Radiol*. doi:10.1016/j.ejrad.2009.03.001.
14. Di Carli, M. F. *et al.* Relationship between CT coronary angiography and stress perfusion imaging in patients with suspected ischemic heart disease assessed by integrated PET–CT imaging. *J. Nucl. Cardiol.* **14**, 799–809 (2007).
15. Gaemperli, O. *et al.* Functionally relevant coronary artery disease: comparison of 64-section CT angiography with myocardial perfusion SPECT. *Radiology* **248**, 414–423 (2008).
16. Hacker, M. *et al.* Sixty-four slice spiral CT angiography does not predict the functional relevance of coronary artery stenoses in patients with stable angina. *Eur. J. Nucl. Med. Mol. Imaging* **34**, 4–10 (2007).
17. Hacker, M. *et al.* Comparison of spiral multidetector CT angiography and myocardial perfusion imaging in the noninvasive detection of functionally relevant coronary artery lesions: first clinical experiences. *J. Nucl. Med.* **46**, 1294–1300 (2005).
18. Rispler, S. *et al.* Integrated single-photon emission computed tomography and computed tomography coronary angiography for the assessment of hemodynamically significant coronary artery lesions. *J. Am. Coll. Cardiol.* **49**, 1059–1067 (2007).
19. Schuijf, J. D. *et al.* Relationship between noninvasive coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. *J. Am. Coll. Cardiol.* **48**, 2508–2514 (2006).
20. Budoff, M. J. *et al.* Diagnostic performance of 64-multidetector row coronary computed

tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J. Am. Coll. Cardiol.* **52**, 1724–1732 (2008).

21. Meijboom, W. B. *et al.* Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J. Am. Coll. Cardiol.* **52**, 2135–2144 (2008).
22. Miller, J. M. *et al.* Diagnostic performance of coronary angiography by 64-row CT. *N. Engl. J. Med.* **359**, 2324–2336 (2008).
23. Leber, A. W. *et al.* Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. *J. Am. Coll. Cardiol.* **47**, 672–677 (2006).
24. Raff, G. L., Gallagher, M. J., O'Neill, W. W. & Goldstein, J. A. Diagnostic accuracy of noninvasive coronary angiography using 64-slice spiral computed tomography. *J. Am. Coll. Cardiol.* **46**, 552–557 (2005).
25. Meijboom, W. B. *et al.* Comprehensive assessment of coronary artery stenoses: computed tomography coronary angiography versus conventional coronary angiography and correlation with fractional flow reserve in patients with stable angina. *J. Am. Coll. Cardiol.* **52**, 636–643 (2008).
26. Nagel, E., Lima, J. A., George, R. T. & Kramer, C. M. Newer methods for noninvasive assessment of myocardial perfusion: cardiac magnetic resonance or cardiac computed tomography? *JACC Cardiovasc. Imaging* **2**, 656–660 (2009).
27. Klocke, F. J. *et al.* ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J. Am. Coll. Cardiol.* **42**, 1318–1333 (2003).
28. Rozanski, A. *et al.* The declining specificity of exercise radionuclide ventriculography. *N. Engl. J. Med.* **309**, 518–522 (1983).
29. Hachamovitch, R. & Di Carli, M. F. Methods and limitations of assessing new noninvasive tests: part I: anatomy-based validation of noninvasive testing. *Circulation* **117**, 2684–2690 (2008).
30. Berman, D. S. & Hachamovitch, R. Risk assessment in patients with stable coronary artery disease: incremental value of nuclear imaging. *J. Nucl. Cardiol.* **3** (Pt 2), S41–S49 (1996).
31. Hachamovitch, R. & Di Carli, M. F. Methods and limitations of assessing new noninvasive tests. Part II: outcomes-based validation and reliability assessment of noninvasive testing. *Circulation* **117**, 2793–2801 (2008).
32. Hachamovitch, R., Hayes, S. W., Friedman, J. D., Cohen, I. & Berman, D. S. A prognostic score for prediction of cardiac mortality risk after adenosine stress myocardial perfusion scintigraphy. *J. Am. Coll. Cardiol.* **45**, 722–729 (2005).
33. Hachamovitch, R. *et al.* Determinants of risk and its temporal variation in patients with normal stress myocardial perfusion scans: what is the warranty period of a normal scan? *J. Am. Coll. Cardiol.* **41**, 1329–1340 (2003).
34. Al-Mallah, M. H., Hachamovitch, R., Dorbala, S. & Di Carli, M. Incremental prognostic value of myocardial perfusion imaging in patients referred to stress single-photon emission computed tomography with renal dysfunction. *Circ. Cardiovasc. Imaging* **2**, 429–436 (2009).
35. Giri, S. *et al.* Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation* **105**, 32–40 (2002).
36. Hakeem, A. *et al.* Predictive value of myocardial perfusion single-photon emission computed tomography and the impact of renal function on cardiac death. *Circulation* **118**, 2540–2549 (2008).
37. Hachamovitch, R., Hayes, S. W., Friedman, J. D., Cohen, I. & Berman, D. S. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* **107**, 2900–2907 (2003).
38. Shaw, L. J. *et al.* The economic consequences of available diagnostic and prognostic strategies for the evaluation of stable angina patients: an observational assessment of the value of precatheterization ischemia. Economics of Noninvasive Diagnosis (END) multicenter study group. *J. Am. Coll. Cardiol.* **33**, 661–669 (1999).
39. Berman, D. S. *et al.* Underestimation of extent of ischemia by gated SPECT myocardial perfusion imaging in patients with left main coronary artery disease. *J. Nucl. Cardiol.* **14**, 521–528 (2007).
40. Bengel, F. M., Higuchi, T., Javadi, M. S. & Lautamäki, R. Cardiac positron emission tomography. *J. Am. Coll. Cardiol.* **54**, 1–15 (2009).
41. Knesaurek, K., Machac, J., Krynyckyi, B. R. & Almeida, O. D. Comparison of 2-dimensional and 3-dimensional ^{82}Rb myocardial perfusion PET imaging. *J. Nucl. Med.* **44**, 1350–1356 (2003).
42. Bateman, T. M. *et al.* Diagnostic accuracy of rest/stress ECG-gated ^{82}Rb myocardial perfusion PET: comparison with ECG-gated ^{99m}Tc-sestamibi SPECT. *J. Nucl. Cardiol.* **13**, 24–33 (2006).
43. Einstein, A. J., Moser, K. W., Thompson, R. C., Cerqueira, M. D. & Henzlova, M. J. Radiation dose to patients from cardiac diagnostic imaging. *Circulation* **116**, 1290–1305 (2007).
44. Di Carli, M. F. *et al.* Clinical myocardial perfusion PET/CT. *J. Nucl. Med.* **48**, 783–793 (2007).
45. Dorbala, S. *et al.* Incremental prognostic value of gated ^{82}Rb-positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *JACC Cardiovasc. Imaging* **2**, 846–854 (2009).
46. Marwick, T. H., Shan, K., Patel, S., Go, R. T. & Lauer, M. S. Incremental value of rubidium-82 positron emission tomography for prognostic assessment of known or suspected coronary artery disease. *Am. J. Cardiol*. **80**, 865–870 (1997).
47. Yoshinaga, K. *et al.* What is the prognostic value of myocardial perfusion imaging using rubidium-82 positron emission tomography? *J. Am. Coll. Cardiol.* **48**, 1029–1039 (2006).
48. Dorbala, S. *et al.* Value of vasodilator left ventricular ejection fraction reserve in evaluating the magnitude of myocardium at risk and the extent of angiographic coronary artery disease: a ^{82}Rb PET/CT study. *J. Nucl. Med.* **48**, 349–358 (2007).
49. Parkash, R. *et al.* Potential utility of rubidium 82 PET quantification in patients with 3-vessel coronary artery disease. *J. Nucl. Cardiol.* **11**, 440–449 (2004).
50. Kribben, A. *et al.* Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J. Am. Coll. Cardiol.* **53**, 1621–1628 (2009).
51. Nandalur, K. R., Dwamena, B. A., Choudhri, A. F., Nandalur, M. R. & Carlos, R. C. Diagnostic performance of stress cardiac magnetic resonance imaging in the detection of coronary artery disease: a meta-analysis. *J. Am. Coll. Cardiol.* **50**, 1343–1353 (2007).
52. Schwitter, J. *et al.* MR-IMPACT: comparison of perfusion-cardiac magnetic resonance with single-photon emission computed tomography for the detection of coronary artery disease in a multicenter, multivendor, randomized trial. *Eur. Heart J.* **29**, 480–489 (2008).
53. Gerber, B. L. *et al.* Myocardial first-pass perfusion cardiovascular magnetic resonance: history, theory, and current state of the art. *J. Cardiovasc. Magn. Reson.* **10**, 18 (2008).
54. Blankstein, R., Rogers, I. S. & Cury, R. C. Practical tips and tricks in cardiovascular computed tomography: diagnosis of myocardial infarction. *J. Cardiovasc. Comput. Tomogr.* **3**, 104–111 (2009).
55. Blankstein, R. *et al.* Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography. *J. Am. Coll. Cardiol.* **54**, 1072–1084 (2009).
56. George, R. T. *et al.* Adenosine stress 64- and 256-row detector computed tomography angiography and perfusion imaging: a pilot study evaluating the transmural extent of perfusion abnormalities to predict atherosclerosis causing myocardial ischemia. *Circ. Cardiovasc. Imaging* **2**, 174–182 (2009).
57. Achenbach, S. Stress computed tomography myocardial perfusion: steps, questions, and layers. *J. Am. Coll. Cardiol.* **54**, 1085–1087 (2009).
58. le Polain de Waroux, J. B. *et al.* Combined coronary and late-enhanced multidetector-computed tomography for delineation of the etiology of left ventricular dysfunction: comparison with coronary angiography and contrast-enhanced cardiac magnetic resonance imaging. *Eur. Heart J.* **29**, 2544–2551 (2008).
59. Schuleri, K. H., George, R. T. & Lardo, A. C. Applications of cardiac multidetector CT beyond coronary angiography. *Nat. Rev. Cardiol.* **6**, 699–710 (2009).
60. van Werkhoven, J. M. *et al.* Prognostic value of multislice computed tomography and gated single-photon emission computed tomography in patients with suspected coronary artery disease. *J. Am. Coll. Cardiol.* **53**, 623–632 (2009).
61. Di Carli, M. F. & Hachamovitch, R. Hybrid PET/CT is greater than the sum of its parts. *J. Nucl. Cardiol.* **15**, 118–122 (2008).
62. Gaemperli, O. *et al.* Cardiac image fusion from stand-alone SPECT and CT: clinical experience. *J. Nucl. Med.* **48**, 696–703 (2007).
63. Berman, D. S. *et al.* Relationship between stress-induced myocardial ischemia and atherosclerosis measured by coronary calcium tomography. *J. Am. Coll. Cardiol.* **44**, 923–930 (2004).
64. He, Z. X. *et al.* Severity of coronary artery calcification by electron beam computed tomography predicts silent myocardial ischemia. *Circulation* **101**, 244–251 (2000).
65. Schenker, M. P. *et al.* Interrelation of coronary calcification, myocardial ischemia, and outcomes in patients with intermediate likelihood of coronary artery disease:

a combined positron emission tomography/computed tomography study. *Circulation* **117**, 1693–1700 (2008).

66. Uebleis, C. *et al.* Stable coronary artery disease: prognostic value of myocardial perfusion SPECT in relation to coronary calcium scoring—long-term follow-up. *Radiology* **252**, 682–690 (2009).
67. Beyer, T. *et al.* A combined PET/CT scanner for clinical oncology. *J. Nucl. Med.* **41**, 1369–1379 (2000).
68. Masood, Y. *et al.* Clinical validation of SPECT attenuation correction using X-ray computed tomography-derived attenuation maps: multicenter clinical trial with angiographic correlation. *J. Nucl. Cardiol.* **12**, 676–686 (2005).
69. Malkerneker, D. *et al.* CT-based attenuation correction versus prone imaging to decrease equivocal interpretations of rest/stress ^{99m}Tc-tetrofosmin SPECT MPI. *J. Nucl. Cardiol.* **14**, 314–323 (2007).
70. Gould, K. L. *et al.* Frequent diagnostic errors in cardiac PET/CT due to misregistration of CT attenuation and emission PET images: a definitive analysis of causes, consequences, and corrections. *J. Nucl. Med.* **48**, 1112–1121 (2007).
71. Goetze, S. & Wahl, R. L. Prevalence of misregistration between SPECT and CT for attenuation-corrected myocardial perfusion SPECT. *J. Nucl. Cardiol.* **14**, 200–206 (2007).
72. McQuaid, S. J. & Hutton, B. F. Sources of attenuation–correction artifacts in cardiac PET/CT and SPECT/CT. *Eur. J. Nucl. Med. Mol. Imaging* **35**, 1117–1123 (2008).
73. Slomka, P. J. *et al.* Comparison of myocardial perfusion ^{82}Rb PET performed with CT- and transmission CT-based attenuation correction. *J. Nucl. Med.* **49**, 1992–1998 (2008).
74. Santana, C. A. *et al.* Diagnostic performance of fusion of myocardial perfusion imaging (MPI) and computed tomography coronary angiography. *J. Nucl. Cardiol*. **16**, 201–211 (2009).
75. Blankstein, R. *et al.* Radiation dose and image quality of prospective triggering with dual-source cardiac computed tomography. *Am. J. Cardiol.* **103**, 1168–1173 (2009).
76. Feuchtner, G. M. *et al.* Radiation dose reduction by using 100 kV tube voltage in cardiac 64-slice computed tomography: a comparative study. *Eur. J. Radiol*. doi:10.1016/j.ejrad.2009.07.012.
77. Hausleiter, J. *et al.* Estimated radiation dose associated with cardiac CT angiography. *JAMA* **301**, 500–507 (2009).
78. Hsieh, J., Londt, J., Vass, M., Li, J., Tang, X. & Okerlund, D. Step-and-shoot data acquisition and reconstruction for cardiac X-ray computed tomography. *Med. Phys*. **33**, 4236–4248 (2006).
79. Husmann, L. *et al.* Feasibility of low-dose coronary CT angiography: first experience with prospective ECG-gating. *Eur. Heart J*. **29**, 191–197 (2008).
80. Abidov, A. *et al.* Clinical effectiveness of coronary computed tomographic angiography in the triage of patients to cardiac catheterization and revascularization after inconclusive stress testing: results of a 2-year prospective trial. *J. Nucl. Cardiol.* **16**, 701–713 (2009).
81. Gaemperli, O. *et al.* Accuracy of 64-slice CT angiography for the detection of functionally relevant coronary stenoses as assessed with myocardial perfusion SPECT. *Eur. J. Nucl. Med. Mol. Imaging* **34**, 1162–1171 (2007).
82. Namdar, M. *et al.* Integrated PET/CT for the assessment of coronary artery disease: a feasibility study. *J. Nucl. Med.* **46**, 930–935 (2005).
83. Kaufmann, P. A. & Gaemperli, O. Combining CT and nuclear: a winning hybrid team. *J. Nucl. Cardiol.* **16**, 170–172 (2009).
84. Rybicki, F. J. *et al.* Initial evaluation of coronary images from 320-detector row computed tomography. *Int. J. Cardiovasc. Imaging* **24**, 535–546 (2008).
85. Min, J. K., Swaminathan, R. V., Vass, M., Gallagher, S. & Weinsaft, J. W. High-definition multidetector computed tomography for evaluation of coronary artery stents: comparison to standard-definition 64-detector row computed tomography. *J. Cardiovasc. Comput. Tomogr.* **3**, 246–251 (2009).
86. Patton, J. A., Slomka, P. J., Germano, G. & Berman, D. S. Recent technologic advances in nuclear cardiology. *J. Nucl. Cardiol.* **14**, 501–513 (2007).
87. Rudd, J. H. *et al.* Imaging atherosclerotic plaque inflammation with ^{18}F-fluorodeoxyglucose positron emission tomography. *Circulation* **105**, 2708–2711 (2002).
88. Nahrendorf, M. *et al.* Nanoparticle PET–CT imaging of macrophages in inflammatory atherosclerosis. *Circulation* **117**, 379–387 (2008).
89. Nekolla, S. G., Martinez-Moeller, A. & Saraste, A. PET and MRI in cardiac imaging: from validation studies to integrated applications. *Eur. J. Nucl. Med. Mol. Imaging* **36** (Suppl. 1), S121–S130 (2009).
90. Judenhofer, M. S. *et al.* Simultaneous PET–MRI: a new approach for functional and morphological imaging. *Nat. Med.* **14**, 459–465 (2008).

Acknowledgments

Désirée Lie, University of California, Irvine, CA, is the author of and is solely responsible for the content of the learning objectives, questions and answers of the MedscapeCME-accredited continuing medical education activity associated with this article.