Noninvasive Assessment of Myocardial Perfusion

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Noninvasive assessment of myocardial perfusion is important in the diagnosis and risk stratification of patients with known or suspected coronary artery disease (CAD). Although single-photon emission computed tomography (SPECT) is most commonly used, multiple modalities including myocardial contrast echocardiography (MCE), positron emission tomography (PET), cardiac MRI (CMR), and cardiac computed tomography (CT) have emerged as promising techniques. This article will critically evaluate the strengths and weakness of these modalities for evaluating myocardial perfusion.

Coronary Physiology

Myocardial perfusion is a highly regulated process that includes epicardial vessels, resistance vessels, and the endothelium. Endothelial dysfunction is an early manifestation of vascular disease and plays a role in the development of CAD. In normal coronaries, sympathetic stimulation causes a flow-mediated endothelium-dependent release of nitric oxide resulting in epicardial and arteriolar vasodilation. With endothelial dysfunction, vasoconstriction from acetylcholine predominates, resulting in an attenuation or absence of the normal flow-mediated vasodilation. When coronary arteries are narrowed by atherosclerotic disease, coronary autoregulation attempts to normalize myocardial blood flow by reducing the resistance of distal perfusion beds to preserve adequate myocardial oxygen supply. A stenosis must exceed 85% to 90% of luminal diameter before significant reductions in resting blood flow occur. However, under vasodilator stimulus, maximal coronary flow has been shown to decrease with stenosis of >45% (Figure 1). This has been demonstrated clinically using quantitative PET myocardial perfusion imaging (MPI). Because perfusion is an early change in the ischemic cascade, stress modalities that assess coronary perfusion reserve have a higher sensitivity in detecting flow-limiting stenoses than analysis of stress-induced wall motion abnormalities or ECG changes alone. Abnormal coronary flow reserve with vasodilator stress in the absence of a significant coronary stenosis occurs and has been attributed to microvascular and/or endothelial dysfunction.

Methods for Inducing Coronary Vasodilation

MPI is based on the ability of stress modalities to induce regional heterogeneity of coronary artery blood flow in the presence of CAD. Exercise induces coronary vasodilation via an endothelium-dependent flow-mediated process to meet the increased oxygen demand. During exercise, in the setting of coronary disease, perfusion reserve may be reduced from flow-limiting stenoses, endothelial dysfunction, and adrenergic stimulation. Exercise is typically associated with a 2- to 3-fold increase in myocardial blood flow and is the preferred modality, as exercise capacity has important prognostic value. Dipyridamole, adenosine, and regadenoson are pharmacological vasodilators that cause arteriolar vasodilation by both direct and endothelium-mediated mechanisms and are associated with a 3.5- to 4-fold increase in myocardial blood flow. Dobutamine, a synthetic β1- and β2-receptor agonist, typically produces a 2- to 3-fold increase in myocardial blood flow similar to exercise.

The Ideal Perfusion Imaging Technique and Agent

Table 1 summarizes the characteristics of an ideal perfusion imaging agent and perfusion imaging modality. An ideal agent would have a high first-pass myocardial uptake proportional to perfusion, insignificant back-diffusion and recirculation, rapid clearance from the blood pool, and kinetics that are not altered by factors such as metabolism or hypoxia. For imaging during first pass, there should be a direct and quantifiable relationship between contrast agent concentration and myocardial perfusion. In both cases, the contrast agent concentration should be proportional to perfusion over a large range of coronary flows. The ideal agent would not alter hemodynamics and would be small in volume compared with the myocardial blood volume. Finally, the agent should be safe, with minimal side effects. The ideal perfusion imaging modality would have a high sensitivity to small changes in coronary blood flow and a quantifiable relationship between signal intensity and perfusion. The technique would have high spatial resolution so that transmural differences in perfusion could be detected. In the case of techniques that image during the first pass of a contrast agent, there should be sufficient temporal resolution to adequately sample the time-intensity curve and provide adequate coverage of the ventricular myocardium. The technique should be reproducible and have a high diagnostic utility and should be free of artifacts that would limit either. Finally, the technique should be widely available, fast and easy to use, and cost-effective.
Our goal will be to critically evaluate each of the perfusion modalities with respect to these ideals.

**SPECT MPI**

Radiotracers

Three radiotracers are commonly used clinically for SPECT MPI. Thallium-201 (Tl-201) is a potassium analog, which is taken up by viable myocytes in proportion to blood flow. However, the low energy of the Tl-201 photon (80 keV) and the long half-life (≈73 hours) are suboptimal for perfusion imaging.14 Tc-99m sestamibi and Tc-99m tetrofosmin bind mitochondrial membranes, show virtually no redistribution after initial uptake, have a 140-keV photon peak that is near the optimal for cameras, and have a 6-hour half-life, permitting injection of higher activity of tracer.15 The first-pass extraction of Tl-201, Tc-99m sestamibi, and Tc-99m tetrofosmin are 86%, 64%, and 54%, respectively, at resting flows.14 However, at high flows when extraction is diffusion-limited, the extraction is considerably lower causing the well-known roll-off phenomenon (Figure 2). Tl-201 has significant delayed redistribution so that stress images should be obtained less than 10 to 20 minutes after stress injection. Imaging of the 3- to 4-hour delayed redistribution permits distinguishing ischemia from scar.16 The Tc-99m perfusion agents take longer to clear from the hepatobiliary system and gut, which may cause scattering of activity into the inferior wall of the heart. All of the agents have properties that allow the stress component and the imaging component to be separated in time and location, which is a significant advantage over other modalities that require imaging during the first pass of the contrast agent. Notably, the uptake of all SPECT tracers is dependent on myocardial cellular integrity in addition to blood flow.

**SPECT MPI Imaging Protocols**

There are a number of SPECT MPI protocols available for the assessment of CAD. With the same-day rest-stress protocol using a Tc99m-labeled perfusion agent, a first injection at rest is followed by imaging roughly 30 minutes later. A second injection with 2 to 3 times the activity is administered during peak stress to overcome the background signal from the rest images, and repeat imaging is performed. A typical Tl-201 protocol would involve injection during peak stress, then imaging roughly 10 minutes later, followed by a redistribution image obtained roughly 4 hours later. A dual-isotope protocol in which Tl-201 is used for the rest images and then a Tc-99m perfusion agent is used during stress soon thereafter has also been used to increase nuclear laboratory throughput.17 However, given the different properties of Tc-99m agents and Tl-201, issues may arise from interpreting rest images with one isotope and stress images with a different isotope. The radiation burden to the patient is higher with dual-isotope imaging (typically 24 mSv) than when using...
rest/stress Tc-99m sestamibi (typically 11 mSv) or Tc-99m–tetrofosmin (typically 8 mSv) alone.\textsuperscript{18}

**Image Analysis**

Images may be analyzed qualitatively using visual analysis or semiquantitatively using differences in relative counts between rest and stress as compared with normal databases. Figure 3 demonstrates the utility of semiquantitative analysis.

**Advantages and Limitations of SPECT**

SPECT MPI is widely available and has been extensively validated. As the stress and imaging components are performed separately, SPECT MPI is compatible with multiple stress modalities including exercise, dobutamine, or vasodilators. Because the imaging does not occur during first pass of a contrast agent, there is less demand for high temporal resolution, and signal-to-noise ratio (SNR) can be improved by collecting data over a longer period of time. SPECT MPI has multiple limitations, including relatively long acquisition protocols and considerably poorer spatial resolution than other available modalities, limiting detection of subendocardial perfusion defects. Furthermore, the roll-off of tracer uptake at higher myocardial blood flows limits sensitivity in detecting mild-to-moderate stenoses.\textsuperscript{15} Additional limitations include motion artifacts related to patient and respiratory motion, scatter and partial volume artifacts in the inferior wall related to gut and biliary activity, and variable attenuation artifacts resulting from breast or subdiaphragmatic attenuation. These artifacts can decrease the diagnostic utility of the perfusion images. Motion artifacts can be corrected in post-processing with the use of motion correction algorithms.\textsuperscript{19} ECG-gated acquisitions, which allow for assessment of regional myocardial function, can be used to help distinguish attenuation artifacts from fixed perfusion defects resulting from myocardial scar. Attenuation correction algorithms that use transmission as well as emission data are available and can improve the accuracy of SPECT MPI.\textsuperscript{20} Within the last few years, developments in novel imaging hardware and iterative reconstruction are leading to improved spatial resolution, contrast, and imaging speed for SPECT MPI.\textsuperscript{21} Because only relative perfusion is generally assessed, SPECT MPI has reduced sensitivity for detecting left main disease or 3-vessel disease related to balanced ischemia.\textsuperscript{22–24} Finally, the tracers expose patients to nontrivial radiation doses, typically 25 mSv for Thallium-201 and 10 to 16 mSv for Tc99m-based agents.\textsuperscript{25}

**Appraisal of the Literature**

 Appropriateness criteria have been published for SPECT MPI and provide guidance for when SPECT MPI should be used for evaluation of myocardial perfusion.\textsuperscript{26} There is an extensive literature evaluating the sensitivity and specificity of SPECT myocardial perfusion imaging for detecting CAD. An analysis of 32 studies including 4480 patients with known or suspected CAD demonstrated mean sensitivity and specificity of 87% and 73%, respectively, for exercise myocardial SPECT for detecting a >50% stenosis.\textsuperscript{27} An analysis of 16 studies of patients with known or suspected CAD including 2492 patients demonstrated sensitivity and specificity of 89% and 75%, respectively, for vasodilator stress with dipyridamole or adenosine for the detection of a >50% stenosis.\textsuperscript{27} In both of these analyses, the prevalence of CAD was high (>75%) and the effects of referral bias were not considered, which generally results in underestimation of the true- and false-negatives and causes an artificial inflation of sensitivity and deflation of specificity. In 12 studies evaluating 721 patients with a low likelihood of CAD (<5% to 10%), the normalcy rate was found to be 91%.\textsuperscript{27} SPECT MPI provides important prognostic information. A meta-analysis, including 19 studies of >39 000 patients with an average of 2.3 years of follow-up, the event rate with a negative SPECT MPI was 0.6%.\textsuperscript{28} However, other studies demonstrate substantially higher event rates in patients with diabetes and/or severe renal disease.\textsuperscript{28,29} The diagnostic approach of SPECT MPI guiding selective coronary angiography reduces costs associated with both diagnosis and revascularization.\textsuperscript{30}

**PET MPI**

Although PET has been used for MPI for greater than 25 years, multiple factors including availability of scanners, increased cost, and reimbursement issues have limited widespread clinical application of PET.\textsuperscript{31} However, the recent
proliferation of hybrid PET-CT scanners may lead to an increasingly important clinical role.

**PET Radiotracers**

N-13 ammonia, Rubidium-82 (Rb-82), and O-15 water are the PET tracers typically used for myocardial perfusion. O-15 water is freely diffusible and has a high first-pass extraction. The uptake is proportional to flow over the largest range of myocardial flows without significant roll-off (Figure 2). O-15 water has a very short half-life of 123 seconds, which makes the agent only compatible with pharmacological stress but enables serial imaging and results in a low overall patient dose (typically \( \approx 2 \text{ mSv} \)). Additionally, the rapid equilibrium between the blood pool and left ventricular cavity requires subtraction techniques for analysis. O-15 is currently not Food and Drug Administration (FDA) approved for MPI. N-13 ammonia has high myocardial retention and fast washout of the blood pool, which make it a good perfusion agent. The increased half-life enables the potential for exercise to be used as the stress modality. Unfortunately, N-13 ammonia still has roll-off of uptake at high coronary blood flow. Both of these agents require an on-site cyclotron for synthesis. The radiation dose from for N-13 ammonia studies are typically 2 mSv. Rb-82 can be eluted from a generator and thus does not require an on-site cyclotron. The disadvantage is that Rb-82 has the most roll-off in uptake of the aforementioned PET tracers and a higher radiation dose (typically 13 mSv). The short half-life makes it most compatible with pharmacological stress but allows for repeated measurements. Recently, new agents based on fluorine-18 (F-18) have been developed that have high cardiac uptake proportional to flow without significant roll-off and good myocardial retention without significant redistribution. Furthermore, the long half-life of F-18 (110 minutes) makes it compatible with multiple stress imaging protocols, and it does not require onsite cyclotron. Clinical studies with this promising tracer are in progress.

**Imaging Protocol**

Typically a resting perfusion image is acquired using either Rb-82 or N-13 ammonia. A bolus of the tracer is given and imaging usually commences between 90 to 120 seconds thereafter. ECG-gated PET acquisition is usually performed for 3 to 6 minutes for Rb-82 and 5 to 15 minutes for N-13 ammonia, owing to their different half-lives. Given these relatively short half-lives, stress imaging can be performed soon after rest imaging. Images at both rest and stress require separate transmission images for attenuation correction. To quantify absolute myocardial perfusion in milliliters per minute per gram, dynamic scanning during first pass of the contrast agent is performed.

**Image Analysis**

Images may be analyzed qualitatively and semiquantitatively, as described above for SPECT imaging. Quantitative analysis can also be performed using data from dynamic acquisitions during first pass of the contrast agent. These methods consist of deriving the arterial input function (AIF) from the blood pool and tissue-activity curves from the myocardium. After correction for partial volume effects, these curves are fit to a 2-compartment kinetic model from which absolute perfusion can be determined. This has been shown to be highly correlated with myocardial blood flow from microspheres in animal models. Figure 4 demonstrates the utility of absolute quantification of perfusion using Rb-82 PET in detecting 3-vessel disease.

**Advantages and Limitations**

PET has improved spatial resolution as compared with SPECT, with spatial resolution of 2 to 3 mm as compared with the 6- to 8-mm resolution of conventional SPECT imaging. PET tracers have significantly less roll-off of extraction at high flows as compared with Tc-99m–based SPECT agents. Unfortunately, Rb-82, which does not require a cyclotron, has the most significant roll-off of the PET perfusion agents. Furthermore, Rb-82 has high positron emission energy and a mean range of 5.5 mm, resulting in a higher dose and lower spatial resolution than N-15 ammonia. Because PET perfusion images are corrected for attenuation as an inherent component of the technology, attenuation artifacts are less of an issue for PET. Furthermore, the tracers used in PET are more easily applied in dynamic scanning to be used for absolute quantification of perfusion. With the recent advances in PET/CT technology, multimodality functional imaging of perfusion with PET combined with anatomic imaging of computed tomographic angio-
phy (CTA) is now possible. The short half-lives of the PET agents result in lower radiation doses than SPECT agents. The major limitations to PET include higher costs and limitations imposed by the need for a cyclotron for all but Rb-82 imaging or imaging agents labeled with F-18. Artifacts from motion during the scan are frequently less apparent, making it harder to evaluate their effects on images. Furthermore, registration artifacts between perfusion images and attenuation maps can result in artifacts. Additionally, when PET is combined with CTA, patients probably will be exposed to even higher radiation doses.

**Appraisal of the Literature**

PET MPI has been extensively evaluated and has been shown to be both sensitive and specific for the diagnosis of CAD. A recent meta-analysis including 14 studies (840 patients) demonstrated a sensitivity of 0.92 (95% CI, 0.90 to 0.94) and specificity of 0.85 (95% CI, 0.79 to 0.90) for the detection of CAD. The average prevalence of CAD in these data sets was 77%, and the studies included both N-13 ammonia and Rb-82 as the perfusion agents.34 There are multiple studies directly comparing the diagnostic utility of PET as compared with SPECT that have demonstrated similar or superior diagnostic accuracy for PET.39,40 A recent article studied 112 patients who underwent Rb-82 PET and 112 patients who underwent SPECT and compared their diagnostic utility, using angiography as the gold standard. The patients were matched for their baseline characteristics, and the cohorts included a subset of patients with low likelihood of coronary disease. On a per-patient basis, PET had a higher diagnostic accuracy (91% versus 76%) and higher specificity (100% versus 66%) for detection of a 50% or greater coronary artery stenosis.37 The summed stress score (SSS) from dipyridamole Rb-82 PET MPI has been shown to have prognostic value in patients with normal or suspected coronary disease. In a study of 367 patients who were followed for an average of 3.1 years, there was an incremental prediction of death and nonfatal myocardial infarction with annual events of 0.4%, 2.3%, and 7% in the normal (SSS <4), mild (SSS, 4 to 7), and moderate to severe (SSS, 8 to 11).41 In another study of 685 patients with a higher prevalence of known CAD (70%), Rb-82 dipyridamole stress demonstrated incremental prognostic value to clinical history and angiographic data. Patients with normal scans had a 90% event-free survival, compared with 87% in patients with small, 75% with moderate, and 76% with extensive defects at 70 months of total follow-up. A normal study was associated with a 0.9% annual event rate, whereas a positive study was associated with a 4.3% annual event rate.42 Additionally, PET has been found to be cost-effective compared with angiography, exercise ECG, and SPECT in terms of quality-adjusted life-years, for a prevalence of CAD <70%.43 Initial studies have begun to assess the potential of hybrid PET-CT imaging protocols.44

**Myocardial Contrast Echo Perfusion**

Although echocardiography for evaluation of exercise- or dobutamine-induced wall motion analysis is commonly used clinically, limitations of the sensitivity of wall motion analysis have led to the development of MCE techniques for assessing perfusion. Unfortunately, the lack of an FDA-approved MCE contrast agent for perfusion has currently put limitations on its widespread clinical application.

**Contrast Agents**

MCE contrast agents are small, gas-filled microbubbles (<10 um) that compress and expand when exposed to an acoustic field and generate strong acoustic backscattering.45 At certain acoustic pressures they undergo nonlinear oscillations that result in generation of harmonic frequencies that can be used to distinguish the signal of the microbubbles from the surrounding tissue. This forms the basis for multiple MCE perfusion techniques.46 The ultrasonic characteristics of the bubbles are related to both the composition of the shell and the encapsulated gas. The microbubbles remain intravascular as they transit the myocardial capillary bed and do not affect cardiac hemodynamics and thus directly reflect myocardial blood flow.47 The intravascular nature of these contrast agents is different from the first-pass cellular uptake of SPECT radionuclide tracers and extravascular diffusion of CT and most MRI contrast agents. The microbubbles must be stable enough to resist destruction from normal ultrasound power outputs to ensure adequate concentrations for imaging but may need to have the ability to rupture with high mechanical index ultrasound for some techniques to measure myocardial perfusion.48

Although ultrasound contrast agents are generally considered safe,49 the FDA issued a black-box warning for Definity and Optison, which, after a 2008 revision, recommends intensive monitoring for patients with pulmonary hypertension or unstable cardiopulmonary conditions and close observation of patients without these conditions. Currently there are no ultrasound contrast agents approved for MCE perfusion imaging, and the FDA considers it to be an experimental procedure.50

**Contrast Echocardiography Perfusion Techniques**

Myocardial perfusion can be assessed with continuous infusion of microbubbles.

When the microbubbles have reached steady-state concentrations, a high mechanical index pulse is used to destroy the bubbles in the imaging plane. The subsequent replenishment of microbubbles is related to myocardial perfusion. Areas that are hypoperfused will have a slower return of microbubbles, whereas areas that are well perfused will have a more rapid return of microbubbles. After the high mechanical index pulse, images can be obtained in a gated intermittent mode with high mechanical index pulses or in a real-time mode with low mechanical index pulses.51 Figure 5 shows MCE perfusion images in a patient with inducible ischemia in both the left circumflex and right coronary artery territories.52 These areas of reduced perfusion agree with the results of coronary angiography. The advantage of the intermittent mode is a higher SNR, but destruction of contrast prevents continuous imaging and thus wall motion cannot be assessed simultaneously. The real-time technique allows simultaneous assessment of both perfusion and wall motion but has a lower sensitivity for microbubble detection.52
perfusion echocardiography has been performed with both vasodilator and inotropic pharmacological stress.

**Image Analysis**
Myocardial contrast echo studies can be analyzed qualitatively or quantitatively. Qualitative analysis is performed by looking for abnormalities in the rate or amount of contrast replenishment after a high mechanical index pulse. Quantitative analysis involves fitting parameters to the time-intensity curves of microbubble replenishment. The reappearance rate of microbubbles is related to myocardial blood flow velocity, and the plateau value is related to the microvascular cross-sectional area. An index of myocardial blood flow is the product of these 2 parameters. Absolute myocardial blood flow can also be determined with knowledge of the myocardial blood volume, which can be assessed as the ratio of the signal intensity of the myocardium to the left ventricular cavity. This has been shown to correlate well with PET-derived blood flow.

**Advantages and Limitations**
MCE has a number of potential advantages over other modalities. MCE has an advantage over SPECT, PET, and CT perfusion imaging because it does not involve ionizing radiation. Compared with SPECT, MCE has improved spatial resolution, enabling detection of subendocardial ischemia. MCE also has the ability to perform absolute quantification of myocardial blood flow. Imaging can be performed during pharmacological stress with inotropes or vasodilators or with exercise. Practical advantages of echocardiography include its wide availability and its relatively low cost. The technique has some limitations. Suboptimal images are obtained in a significant number of patients as the result of respiratory motion, body habitus, or lung disease. Attenuation from the microbubbles may result in artifacts in the basal segments of the left ventricle. These factors can limit image quality and adequate spatial coverage of the ventricle, resulting in increased variability and decreased reproducibility. Furthermore, there are some operator-dependent factors such as maintaining a constant image plane during replenishment of microbubbles. Finally, there are no FDA-approved contrast agents for MCE perfusion.

**Appraisal of Literature**
A number of studies have demonstrated a high concordance of stress perfusion echocardiography and SPECT. A meta-analysis of 9 studies including 588 patients comparing SPECT with perfusion stress echocardiography demonstrated an average concordance of 81%. Multiple studies have also demonstrated comparable accuracy to SPECT for diagnosing CAD. The overall sensitivity and specificity of MCE from a meta-analysis of 18 studies including 1088 patients demonstrated a sensitivity of 82% and specificity of 80%. In a retrospective study of 788 patients, MCE was shown to have prognostic value that was incremental to left ventricular ejection fraction.

**CMR Perfusion Imaging**
Over the last few years, improvements in hardware, pulse sequence development, and image reconstruction algorithms have enabled high-resolution imaging of first-pass myocardial perfusion with CMR.

**Contrast Agents**
Most CMR studies of myocardial perfusion are based on the first-pass of a bolus of gadolinium-DTPA contrast agents. Interactions between the unpaired electrons of paramagnetic gadolinium and water protons in close proximity result in more rapid relaxation of these water protons. Thus, the gadolinium is being detected indirectly via its effect on the relaxation of protons. The T₁ and T₂ relaxation times of water protons are inversely proportional to the local gadolinium concentration. Therefore, areas that are well perfused will have a shorter T₁ and appear bright on heavily T₁-weighted images, whereas regions that are hypoperfused will have longer T₁ and will appear hypointense. The T₁ of the myocardium is affected by multiple factors, including the extraction fraction of the contrast agent as well as water exchange between the intravascular, extravascular, and extracellular spaces. The extraction fraction is typically 0.5 to 0.6 for extracellular, extravascular contrast agents, which are small molecules that freely diffuse out of the vascular space. Quantification of myocardial perfusion is possible by methods that take these factors into account. Intravascular contrast agents exist and have been applied to MPI. These agents are usually confined to the intravascular space because of their...
large size and have higher relativity.\textsuperscript{61} Recently, the first gadolinium-based intravascular agent was approved for magnetic resonance angiography.

Data Acquisition Pulse Sequences

Requirements of a first-pass CMR perfusion imaging pulse sequence include strong T\textsubscript{1} weighting to impart contrast related to the contrast agent concentration, rapid data acquisition to obtain images at multiple slice locations per R-R interval, adequate spatial resolution to detect subendocardial perfusion abnormalities, and minimal artifacts to maximize diagnostic utility. The relationship between signal intensity and underlying blood flow is affected by the choice of pulse sequence parameters. Recent studies have used nonselective saturation recovery (SR) pulse sequences, which are well suited for multislice imaging, insensitive to variations in heart rate, and enable shorter preparation times than inversion recovery (IR)-prepared pulse sequences.\textsuperscript{62} The disadvantages of SR are its reduced dynamic range as compared with IR preparation. The saturation time is an important determinant of the linearity of T\textsubscript{1} to signal intensity. At shorter saturation times, the signal intensity is more linearly related to T\textsubscript{1} but the SNR is generally lower. At longer saturation times the SNR is higher, but there is a loss of linearity, especially at higher contrast agent concentrations.

To maximize temporal resolution and spatial coverage, SR preparations are combined with a variety of rapid readout techniques including fast low-angle shot (FLASH),\textsuperscript{63} echoplanar imaging,\textsuperscript{64} or steady-state free precession (SSFP).\textsuperscript{65} The advantages of FLASH include reduced susceptibility-induced image artifacts; disadvantages include lower achievable SNR and longer readout duration. The advantage of SSFP sequences is higher SNR, but at the cost of increased susceptibility artifacts. Echoplanar imaging techniques have the highest temporal resolution but may have ghosting artifacts resulting from periodic fluctuations of the k-space signal. Multiple studies have compared these techniques, but, regarding the optimal protocol, there has been no clear consensus in the field. To further improve temporal resolution, all of the above techniques have been combined with parallel imaging techniques.\textsuperscript{66} Parallel imaging with acceleration factors of 2 is now routinely used in clinical practice, and multiple highly accelerated techniques have begun to be applied in human studies.

Many investigators have performed perfusion studies at 3 T and have demonstrated improved SNR and CNR.\textsuperscript{67} Recently, 3D encoding methods have been combined with parallel imaging to improve spatial coverage using either 3D SSFP or 3D FLASH.\textsuperscript{68}

Imaging Protocol

Stress perfusion CMR is generally applied as part of a comprehensive study that evaluates ventricular function, stress and rest perfusion, and viability/myocardial infarction. Cine images to assess ventricular function are obtained generally in <10 minutes. Stress perfusion images are then obtained during infusion of 140 \(\mu\)g/kg/min of adenosine for 2 to 4 minutes. Typically, 3 to 4 short-axis perfusion images are acquired each heart beat during the injection of 0.05 to 0.1 mmol/kg gadolinium contrast at a rate of 3 to 4 mL/s via a power injector during first pass of the contrast agent. Forty to 60 image frames are usually obtained. After a 10-minute contrast washout period, perfusion images are obtained at rest using the same imaging protocol. Finally, late gadolinium-enhanced images are obtained covering the heart. The study typically takes approximately 45 to 60 minutes in experienced centers.

To perform quantitative perfusion, the AIF at rest and stress must also be determined. Accurate determination of the AIF requires a low contrast dose to avoid T2\textsuperscript{*} saturation effects. Three approaches have been used: using a lower dose of contrast (0.05 mmol/L) for the whole perfusion study, performing separate injections during stress and rest with very low contrast doses (0.0025 mmol/kg), or using a hybrid perfusion sequence that obtains a separate image for the AIF on each heartbeat.

Image Analysis

Images can be evaluated qualitatively using visual analysis. Klem et al\textsuperscript{69} reported an algorithm with high sensitivity and specificity for detecting CAD. First late gadolinium-enhanced images are reviewed for evidence of prior myocardial infarction, then the stress images are evaluated for inducible ischemia, and finally the rest images are reviewed to assess for artifacts. This technique has an overall sensitivity and specificity of 89\% and 87\%, respectively, for detecting CAD.\textsuperscript{69} The high spatial resolution of CMR enables the detection of subendocardial ischemia. In a patient with 3-vessel disease, the subendocardial ischemia is clearly seen on the CMR study, whereas it is not evident on the SPECT MPI study (Figure 6). Images can also be analyzed using a semiquantitative approach using the time-intensity curves during the first pass of signal through the myocardium. Parameters such as the upslope, time to peak, and peak myocardial enhancement have been used to evaluate for areas with reduced perfusion. Absolute quantification of myocardial perfusion can be obtained from the time-intensity curves of the myocardium AIF using deconvolution (Figure 7).\textsuperscript{70}

Advantages and Limitations

Cardiac MRI has significant advantages for perfusion stress testing, including its high spatial resolution, the ability to perform absolute quantification of perfusion, and the additional information provided in a comprehensive CMR study. Furthermore, the study can be performed rapidly, has limited operator dependence, and the signal characteristics are largely independent of the patient’s body habitus. CMR perfusion studies have adequate spatial coverage and temporal resolution that continue to improve with further advances in parallel imaging techniques. Current pulse sequences suffer from a “dark-rim” artifact that can be mistaken for a true perfusion abnormality.\textsuperscript{82} The origin of this artifact probably is multifactorial, including myocardial motion during data acquisition, Gibbs ringing caused by resolution limitations, or susceptibility artifacts from the passage of the contrast agents.\textsuperscript{65,71,72} As compared with a true perfusion abnormality, this artifact tends to be present transiently at peak ventricular cavity enhancement. Because imaging occurs during first
pass of a contrast agent, CMR perfusion imaging is most compatible with vasodilator stress. For multiple reasons, gadolinium-DTPA is not an ideal contrast agent. It has intermediate extraction fraction during first-pass imaging and has nonlinearity in the relationship between signal intensity and perfusion. In regions of infarction, gadolinium has a slow washout that changes the baseline signal intensity for the rest perfusion study; however, the combination of perfusion with delayed enhancement imaging enables accurate detection of myocardial infarction. Recently, gadolinium contrast agents have been associated with a rare but serious condition called nephrogenic systemic fibrosis, which primarily occurs in patients with significant reductions in creatinine clearance.73 The FDA has issued a black-box warning for gadolinium-based contrast agents in patients with a creatinine clearance <30 mg/dL.

Appraisal of the Literature
Appropriateness criteria have been established for CMR that provide guidance to the appropriate use of CMR perfusion imaging and stress testing.74 Adenosine stress cardiac MRI has been shown to be both sensitive and specific for detection of CAD. A recent meta-analysis including 1516 patients with intermediate likelihood of disease (prevalence 57.4%) undergoing adenosine stress perfusion MRI demonstrated a sensitivity of 0.91 (95% CI, 0.88 to 0.94) and specificity of 0.81 (95% CI, 0.77 to 0.85).75 As CMR perfusion is still a relatively new modality, there is less prognostic data as compared with other modalities. In a study of 420 patients with known or suspected CAD, the presence of abnormal perfusion was associated with a 17% event rate, whereas a normal perfusion study was associated with a 5% event rate.76 In a study of 135 patients presenting to the emergency

Figure 6. SPECT MPI (left) and CMR first-pass perfusion images (right) at stress and rest in a patient with suspected coronary disease. The superior spatial resolution of the CMR study enables clear visualization of subendocardial ischemia in this patient who was found to have 3-vessel disease at coronary angiography.

Figure 7. First-pass CMR perfusion image demonstrates a large perfusion defect in the inferolateral wall (yellow arrow). This is seen on the time-intensity curves from the region of the perfusion abnormality and remote myocardium (purple arrow). By deconvolution of the tissue functions from the AIF (green curve) absolute myocardial blood flow can be determined. Adapted from Patel A, et al. J Nucl Cardiol. 2008;15,5:698–708.
department with chest pain and negative troponin-I, there were no events in 107 patients without CMR perfusion abnormalities at 1 year, and the presence of an abnormal stress CMR was significantly predictive of MACE.\textsuperscript{77} Absolute perfusion reserve by CMR perfusion is highly correlated with values obtained by PET in human subjects.\textsuperscript{78} CMR perfusion has also been shown to correlate with fractional flow reserve by cardiac catheterization.\textsuperscript{79} A multicenter dose-ranging trial of 234 patients randomly assigned subjects to receive 1 of 5 gadolinium contrast doses and directly compared CMR stress perfusion and SPECT MPI using coronary angiography as the gold standard. Perfusion CMR at the optimal CM dose (0.1 mmol/kg) had a performance similar to SPECT, if only the SPECT studies of the 42 patients with this dose were considered; however, the diagnostic performance of perfusion CMR was superior as compared with the entire SPECT population (N=212), which requires further evaluation in larger prospective trials with standardized methodology.\textsuperscript{80}

CTA Perfusion Imaging

With the recent advances in multidetector CT (MDCT) and CT coronary angiography, there has been renewed interest in using CT to evaluate myocardial perfusion.

Contrast Agents

Myocardial perfusion imaging with CT is based on the intravenous injection of iodinated contrast agents that increase the absorption of x-rays in proportion to the concentration of iodine.\textsuperscript{81} Most of the agents used clinically are nonionic contrast agents with a high iodine concentration.\textsuperscript{82} Iodinated contrast agents are not hemodynamically inert and have an influence on coronary blood flow, inducing a reduction in coronary flow followed by a hyperemic response.\textsuperscript{83} This effect is less significant, however, for low osmolarity nonionic contrast agents.\textsuperscript{84} During first pass, there is also significant diffusion of the contrast agents into the interstitial space, particularly for nonionic and low-molecular-weight compounds.\textsuperscript{85} The first-pass extraction of contrast is around 33% with maximal vasodilation and is substantially higher at lower flow rates.\textsuperscript{85} Thus, for accurate assessment of perfusion, the extravascular diffusion of the agent must be taken into account. Methods for correcting for this effect have been applied.\textsuperscript{86} In terms of safety, the major concern is contrast-induced nephropathy, especially in patients with reduced renal function (creatinine clearance <60).\textsuperscript{87}

Imaging Techniques

Multiple studies have evaluated perfusion in myocardial infarction, but to date there are only a few published studies that have evaluated myocardial perfusion to detect inducible ischemia with vasodilator stress. Kurata et al\textsuperscript{88} performed ECG-gated contrast-enhanced coronary CTA protocols during adenosine stress and 20 minutes later at rest and visually assessed for areas of inducible ischemia in 12 patients without known CAD and demonstrated high concordance (0.83) with conventional SPECT in localizing territories of inducible ischemia. A comparison between CTA perfusion, SPECT, and angiography is shown in Figure 8. Kido et al\textsuperscript{89} performed dynamic cine 16-detector MDCT during adenosine infusion in 14 patients with intermediate risk of CAD. Images were obtained continuously for 20 seconds at a midventricular level, and myocardial blood flow was quantified. Coronary angiograms and SPECT stress studies were also obtained. In territories with significant coronary stenosis by angiography, there was significantly reduced myocardial blood flow. Their study had a 72% sensitivity and 80% specificity for detecting a significant coronary stenosis with a myocardial blood flow cutoff of 1.5 mL/min/g.\textsuperscript{89} George et al\textsuperscript{90} performed adenosine stress coronary CTA using a 64-detector MDCT in an animal model of left anterior descending coronary artery stenosis. They detected a significant reduction in signal density of the myocardium in the left anterior descending coronary artery territory as compared with remote regions. Furthermore, they demonstrated a nonlinear correlation of the ratio of the signal density in the myocardium normalized to the left ventricular cavity signal density. George et al\textsuperscript{91} also evaluated the use of dynamic perfusion imaging in a dog model of left anterior descending coronary artery stenosis using 64-detector MDCT. After adenosine infusion, dynamic CT images covering 32 mm of the left ventricle were obtained continuously for 70 seconds.
They demonstrated a strong correlation between absolute perfusion by MDCT and microspheres. Nagao et al performed cardiac MDCT at rest and SPECT MPI at rest and stress in 34 patients with suspected coronary disease. They found that systolic endocardial signal density in regions with inducible ischemia by SPECT MPI was significantly lower than in nonischemic regions. Recently, George et al performed adenosine stress CT perfusion imaging in 40 patients using 64- or 256-detector MDCT. They demonstrated that the combination of CT perfusion and angiography detected perfusion abnormalities with a sensitivity and specificity of 86% and 92%, respectively, as compared with a combination of coronary angiography and SPECT MPI. In their study, the radiation dose for 64-detector MDCT was 16.8 mSv (stress only) and 21.6 mSv with 256-detector MDCT (stress and rest); however, doses may be lower with 320-detector, prospectively gated acquisitions.

There has also been a recent report of using dual-energy CT (DECT) on a dual-source MDCT scanner to determine regional myocardial perfusion. DECT relies on the fact that iodinated contrast agents have unique absorption of x-rays of different energy levels that enables mapping of the iodine concentration. Ruzsics et al performed dual-energy CTA in 35 patients with known or suspected CAD. Iodine distribution maps were determined from the image sets with different x-ray energies. In 16 patients, stress/rest SPECT was also performed. In the 5 patients with fixed defects, DECT correctly identified 90% of the perfusion defects, and in the 11 patients with reversible defects, DECT correctly identified 88% of the defects on a per-defect basis. It is interesting that DECT imaging at rest correlated with inducible ischemia by stress/rest SPECT; however, the physiology underlying this observation requires further investigation.

Advantages and Limitations
The advantages of MDCT include its high spatial resolution, rapid data acquisition, and the ability to potentially combine information of coronary anatomy, ventricular function, and perfusion in one study. Furthermore, with the growth of CTA, MDCT scanners are becoming widely available. Absolute quantification of CT perfusion has been demonstrated for dynamic studies but requires modeling of the effects of contrast diffusion into the extravascular space. Furthermore, advancement of MDCT with 256 or 320 detectors may enable dynamic analysis of perfusion with high temporal resolution. However, the use of MDCT for perfusion analysis has multiple limitations. Because image quality is inversely related to heart rate, the increase in heart rate with vasodilator stress may compromise image quality. Furthermore, artifacts such as beam-hardening result in variations of signal intensity within the myocardium, limiting the ability of quantitative assessment of perfusion. The contrast agent doses typically used preclude evaluation of patients with significant renal insufficiency. The main disadvantage of assessing perfusion with MDCT is the potentially high doses of ionizing radiation. Protocols that involve obtaining CTA studies at rest and stress would potentially double the current coronary CTA radiation dose. Dynamic perfusion analysis probably would have an even higher radiation dose. As MDCT continues to evolve, further studies of perfusion using this technique are warranted.

Table 2. Pooled Diagnostic Performance of Perfusion Imaging Techniques

<table>
<thead>
<tr>
<th>Modality</th>
<th>n</th>
<th>CAD Prevalence</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECT</td>
<td>4480</td>
<td>76%</td>
<td>0.87 (0.86–0.88)</td>
<td>0.73 (0.70–0.76)</td>
</tr>
<tr>
<td>PET</td>
<td>1442</td>
<td>77%</td>
<td>0.85 (0.79–0.90)</td>
<td>0.87 (0.84–0.90)</td>
</tr>
<tr>
<td>CMR</td>
<td>1516</td>
<td>57%</td>
<td>0.91 (0.88–0.94)</td>
<td>0.81 (0.77–0.85)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>1088</td>
<td>69%</td>
<td>0.82 (0.76–0.88)</td>
<td>0.80 (0.73–0.87)</td>
</tr>
</tbody>
</table>

Summary
There has been significant progress in the noninvasive evaluation of myocardial perfusion over the last 30 years. The currently available modalities each have their advantages and limitations, as described in this article, but no technique has demonstrated unequivocal superiority (Table 2). Advances in quantitative methods are continuing to improve diagnostic accuracy in patients with left main and 3-vessel disease who are most likely to benefit from revascularization over medical therapy. It is vitally important to develop methodologies that permit measurement of absolute flow in milliliters per minute per gram or flow reserve from rest to stress states. Presently, the radionuclide techniques as used clinically only assess relative flow differences between regions of myocardium. Integration of anatomic and functional information from 1 or multiple modalities in the form of multimodality imaging with fusion of 2 disparate images (eg, CMR with PET) is becoming increasingly important as well. Future studies should adopt a functional gold standard, such as fractional flow reserve, in addition to the anatomic gold standard of coronary stenosis severity. This is especially relevant to our understanding of microvascular dysfunction, resulting in reductions in perfusion reserve without angiographically significant coronary stenoses. Additionally, in the era of escalating medical costs, we must determine the value of the accurate noninvasive assessment of perfusion, as a means of controlling costs for expensive and invasive procedures such as coronary angiography and unnecessary revascularization. Appropriateness criteria for perfusion stress testing have been established for SPECT and CMR and should be established for PET, contrast echocardiography, and CT perfusion, as well as other new imaging techniques as they become established into clinical practice. Cost-effectiveness of the new technologies must be evaluated. It is no longer sufficient to provide test performance only as compared with established techniques but rather to determine whether they significantly affect patient treatment and ultimately patient outcomes. Outcomes studies demonstrating the worth of
imaging of myocardial perfusion are being demanded. Advances in technology are continuing to improve the diagnostic and prognostic utility of noninvasive assessment of myocardial perfusion and are enhancing the ability to risk-stratify patients for targeted personalized therapy.

Disclosures

None.

References


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Noninvasive Assessment of Myocardial Perfusion

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