Review Article

Myocardial Perfusion Imaging: A Brief Review of Nuclear and Nonnuclear Techniques and Comparative Evaluation of Recent Advances

Abstract

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Invasive coronary angiography (ICA) is the gold standard for the evaluation of epicardial CAD. In the pathogenesis of the CAD, myocardial perfusion abnormalities are the first changes that appear followed by wall motion abnormalities, electrocardiogram changes, and angina. Myocardial perfusion imaging (MPI) demonstrates the cumulative effect of pathology at epicardial coronary arteries, small vessels, and endothelium. Thus, it evaluates the overall burden of ischemic heart disease (IHD). MPI is used noninvasively to diagnose early asymptomatic CAD or to know the functional significance of known CAD. There are evidence that early detection of myocardial perfusion abnormalities followed by aggressive intervention against cardiovascular risk factors may restore myocardial perfusion. This may lead to reduce morbidity and mortality. Various MPI modalities have been used to diagnose and define the severity of CAD. Cardiac myocardial perfusion single-photon emission computed tomography (myocardial perfusion scintigraphy [MPS]) has been in use since decades. Several newer modalities such as positron emission tomography, cardiac magnetic resonance imaging, computed tomography perfusion, and myocardial contrast echocardiography are developing utilizing the similar principle of MPS. We shall be reviewing briefly these modalities, their performance, comparison to each other, and with ICA.

Keywords: *Cardiac magnetic resonance imaging, cardiac myocardial perfusion single-photon emission computed tomography, computed tomography perfusion, coronary artery disease, invasive coronary angiography, myocardial contrast echocardiography, positron emission tomography*

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Introduction

Cardiovascular disease remains the leading cause of death in the world.[1] After the age of 40 years, nearly half of the men and one-third of women may develop coronary artery disease (CAD).[2] Invasive coronary angiography (ICA) remains gold standard for the diagnosis of the epicardial CAD. However, a significant proportion of patients referred for coronary angiography are found to have no significant obstructive coronary disease.[3] ICA is not found to be a cost-effective first-line investigational strategy when the pretest probability of significant CAD is <75%.[4] It is also a well-established fact that anatomical stenosis severity may not correlate with physiological severity absolutely.[5] Both the American and European guidelines have emphasized the functional imaging in the patients having an intermediate pretest probability of CAD.[6,7] Various noninvasive imaging techniques are used to investigate the presence of stress-induced ischemia in patients with known or suspected CAD, such as myocardial perfusion scintigraphy [MPS], positron emission tomography (PET), myocardial contrast echocardiography (MCE), cardiac magnetic resonance (CMR), and computed tomography perfusion (CTP).

Imaging Techniques

Nuclear myocardial perfusion imaging-myocardial perfusion scintigraphy and positron emission tomography

Cardiac MPS and PET imaging are done after physical or pharmacologic stress and at rest to determine regional differences in coronary blood flow. They provide a qualitative and semi-quantitative assessment of regional perfusion defects.[8] MPS has been extensively used in clinical practice since more than three decades and extensive literature available in support

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of its diagnostic performance, value in risk stratification, and prognostication. Myocardial perfusion imaging (MPI) tracers show the linear relationship between peak stress myocardial blood flow (MBF) and myocardial tracer concentration uptake. However, this is hampered in clinical practice by the "roll-off phenomenon" in which increases in coronary flow beyond 1.5–2-fold are not accompanied by a directly proportional increase in tracer uptake. MPS detects ischemia if the stenosis is capable of producing a reduction in blood flow. This happens only when the diameter of stenosis is in excess of ~50%–70%. Early published literature (analysis of 79 studies of nearly 9000 patients), MPS reported a sensitivity of 86% and specificity of 74% for detecting more than 50% angiographic stenosis.[9]

It provides an incremental value for risk assessment in patients with known or suspected CAD. There is a linear risk of cardiac death and MI associated with increasing extent and severity of perfusion abnormalities. In large meta-analysis comprising of nearly 40,000 patients, a normal or low-risk MPS study was associated with a low major adverse cardiovascular event rate (0.6% per year). This is comparable to event rates in the general population without evidence of CAD.[10] A recent prospective study has shown that an abnormal scan predicts a multifold increase in the rates of death (9.2% vs. 2.6%), death or MI (11.8% vs. 3.3%), and revascularization (24.7% vs. 2.7%).[11] Extent and severity of stress perfusion abnormality also predict high rates of MI and death. A summed stress score of >13 was found associated with a high (4.2%) annual risk of MI.[12]

MPS is an excellent prognostication tool. In a large observational study, including 10,627 patients with suspected CAD, it was found that patients with no or a mild stress-induced ischemia have a survival advantage with medical therapy. However, in patients with extensive ischemia (>10%–12.5%) survival benefit with revascularization was noted.[13] There is a strong association between the extent and severity of hibernating myocardium, posttest treatment, and subsequent patient survival. Patients with limited hibernating myocardium benefit from the medical therapy and while those with extensive hibernating myocardium (>10%) may have benefited from revascularization.[14]

Similarly, for preoperative risk stratification, MPS has an excellent high negative predictive value. A normal preoperative MPS result incurs not only a low perioperative risk and but even a low long-term risk.[15] A recently published large retrospective observational study of 322,688 patients undergoing noncardiac surgery concluded that abnormal myocardial perfusion appears to be an important risk factor for adverse postoperative events.[16]

In contrast to angiography, MPS identify only coronary territory supplied by the most severe stenosis. It may be a less sensitive technique to delineate the full extent of cardiac atherosclerotic burden, especially in the setting of multivessel disease. This is an area where PET MPI holds great potential. The superior quality and accuracy of PET in comparison to MPS has been attributed to its better spatial resolution and attenuation correction.[17] PET MPI provides absolute quantitation of MBF and coronary flow reserve (CFR). CFR is the ratio of hyperemic to rest MBF and is an integrated measure of coronary vasomotor dysfunction. It measures holistic effect of focal, diffuse, large, small-vessel CAD, and endothelial dysfunction on myocardial perfusion.[5] It gives a complete insight of IHD rather than CAD alone.

In a meta-analysis including 177 studies with nearly 12,000 patients confirmed higher sensitivity of PET relative to MPS (92.6% vs. 88.3%) for the detection of >50% epicardial stenosis, however with comparable specificity.[18] However, the clinical effect of this difference may be small. Another meta-analysis of 114 MPS and 15 PET studies demonstrated similar results.[19] CFR measurements by PET can distinguish patients at low or high risk for serious adverse events, including cardiovascular death, beyond comprehensive clinical assessment, left ventricular ejection fraction, or traditional semi-quantitative measures of stress-induced ischemia. It also helps in risk-reclassification (~ 35% of patients) of intermediate risk patients. CFR of <2 and <1.5 has been associated with a 3.4 and 5.6 fold increased risk of cardiac death.[20]

A lot of the latest research has advanced gamma camera performance. Recently, introduced gamma camera systems with optimized acquisition geometry, collimator designs, and advanced reconstruction techniques have the potential to further improve image quality.[21] Cadmium-zinc-telluride (CZT) detectors have superior energy and spatial resolution. They have demonstrated a sensitivity of 95% and accuracy of 69% for detecting obstructive CAD.[22] These cameras are more sensitive therefore require a shorter imaging time even at lesser radioactivity administration.[23] CZT camera provides very fast perfusion imaging and allows the acquisition of serial dynamic images. Thus, it allows measurement of MBF and CFR. Hybrid imaging cameras provide a fusion of anatomical and functional images, i.e., MPS/coronary computed tomography angiography (CCTA). A meta-analysis comprising of 951 patients and 1973 vessels have demonstrated improved diagnostic specificity of hybrid imaging for the detection of obstructive CAD in comparison to stand-alone CCTA.[24] Patients with a normal MPS study who underwent concomitant CCTA, an abnormal CCTA was associated with a higher event rate.[25]

PET/CCTA offers an accurate spatial coregistration of myocardial perfusion defect and subtending coronary artery. Javadi *et al*. found that 72% (51/71) of the patients demonstrated differences from the standard assignment in

at least one myocardial segment; 112 of 1207 segments were reassigned to nonstandard vascular territories. Due to variability in the coronary tree, the vascular territory distribution can be done more accurately by CCTA.[26] A study comparing CCTA with MPS/CCTA hybrid imaging has demonstrated poor specificity and positive predictive value (PPV) of CCTA alone. Hybrid imaging approach resulted in a significant improvement in specificity (from 63% to 95%) and PPV (from 31% to 77%) in comparison to CCTA.[27]

Myocardial contrast echocardiography

Echocardiography has been used since a long to study anatomy and function of the heart. Lipid microspheres are used as echocardiographic contrast agent. These microspheres vary according to their outer shell composition (hydrophilic properties) and gas content (echogenic properties). Once microspheres are injected into the systemic circulation, the ultrasound-induced oscillation reflects a unique echo that allows differentiation of blood, myocardium, and other tissues.[28] After opacification of the left ventricle cavity with contrast, a high-intensity ultrasound pulse causes destruction of the microspheres. In normal myocardium, replenishment of the left ventricle contrast takes ~5 s. Under hyperemic conditions, contrast replenishment typically takes <2 s. Decreased MBF due to coronary stenosis results in an increased replenishment time.[29]

MCE has shown good diagnostic performance in comparison with ICA. It has shown a sensitivity of 83% and specificity of 80% (meta-analysis of ~1700 patients from 20 trials) for the diagnosis of CAD.[30] MCE has demonstrated reasonable concordance with MPS (kappa 0.81 at the patient level and 0.86 at the vessel level) for the diagnosis of CAD.[31] MCE also provides important prognostic data. In a study by Tsutsui *et al*., abnormal myocardial perfusion determined by MCE was a better predictor of cardiac events than other clinical factors, ejection fraction, and wall motion abnormalities. The 3-year event-free survival in patients with normal wall motion and myocardial perfusion was 95% compared to 68% in patients with abnormal wall motion and myocardial perfusion.[32] Another study of patients with known or suspected CAD who underwent MCE has shown a hazard ratio of 6.1 for major adverse cardiovascular events in patients with any inducible perfusion defect or wall motion abnormality.[33] In patients suspected of the acute coronary syndrome with normal troponin levels and non-diagnostic electrocardiogram, presence of abnormal wall motion and myocardial perfusion yielded a hazard ratio of 10.7 for prediction of future cardiac events.[34] CFR measure by MCE is also useful in the evaluation of patients with microcirculatory disease and has shown to discriminate ischemic from nonischemic cardiomyopathy.[35]

Cardiac magnetic resonance imaging

CMR has been increasingly utilized in clinical cardiology over the past 2 decades. This technique uses pharmacological stress by a vasodilator (adenosine or regadenoson) or by dobutamine. Vasodilator methods involve the administration of intravenous gadolinium contrast during vasodilator infusion that leads to perfusion defects in ischemic territories during hyperemia. CMR also demonstrate wall motion abnormalities in the presence of ischemia.[36] CMR assessment is usually qualitative, with visual assessment for the presence and extent of ischemia. However, to improve diagnostic accuracy, quantitative measurement of perfusion has been done. These methods are either semi-quantitative that uses the difference in signal intensity between areas of the myocardium, or fully quantitative that measure absolute blood flow.[37]

In a study of 84 patients, who underwent rest and vasodilator stress imaging, the measurement of myocardial perfusion reserve using CMR was found to have a sensitivity of 88% and specificity of 90%, in comparison with ICA.[38] It has shown excellent agreement with PET for the detection of obstructive epicardial CAD.[39] In a recent meta-analysis comparing CMR, PET, and MPS have shown that all have similar sensitivity with various specificity. CMR showed a sensitivity of 89% and specificity of 76% compared to ICA and appeared to have a better diagnostic accuracy than MPS.[19] MR-IMPACT trial, CE-MARC trial, and MR-IMPACT II trials compared CMR with MPS in the diagnosis of stable angina with a gold standard of ICA. They have shown CMR have a superior diagnostic accuracy in comparison to MPS. This was noted in both sexes.[40-42] In CE-MARC 2 trial, patients were randomized to a CMR-guided strategy, MPS, or the UK National Institute for Health and Care Excellence guideline recommendation. Authors found that CMR was equivalent to MPS and that both strategies reduced unnecessary ICA.[43]

In MR-INFORM trial, investigator compared adenosine stress CMR with Fractional Flow Reserve (FFR) in patients with suspected stable angina. CMR was found to be noninferior to FFR, with both conferring ≤4% risk of major adverse cardiovascular events within 1 year.[44] Recent meta-analysis reported a sensitivity of 89% and specificity of 87% at the per-patient level compared to FFR. The performance of CMR was found equivalent to CT and PET.[45] Normal dobutamine stress CMR predicts a 3-year event-free survival of 99.2%. It was found to be an effective and robust tool for patients of either sex.[46] CMR imaging also provides effective risk stratification. A meta-analysis of 56 studies including 25,497 patients who underwent CMR imaging has been done. Researchers found that CMR findings such as wall motion abnormalities, stress-induced perfusion defects, and low LVEF were associated with increased risk of adverse events including all-cause death.[47] CMR is currently accepted as the

noninvasive gold standard for the assessment of cardiac structure and function. It allows better assessment of wall motion abnormalities as well as provide superior diagnostic information in comparison to echocardiography.[48]

Computed tomography perfusion

CT perfusion uses a similar principle as used by other MPI modalities. A multidetector CT system images in a dynamic mode and sequential images are obtained over a period to record the kinetics of iodinated contrast in the arterial blood pool and the myocardium.[49] Areas of infarction or ischemia appear hypodense in comparison to normal myocardium. George *et al*. used 64-detector CT in a canine ischemia model and performed CTP during adenosine infusion. They found strong correlations between the ratio of myocardial to left ventricular upslope and microsphere-derived MBF. The authors replicated the study in humans using adenosine stress on 64 and 256-row CT scanner. They did CCTA and measured CTP. In comparison to combined ICA and MPS, a Combined CCTA/CTP was found 86% sensitive and 92% specific for identifying atherosclerosis causing perfusion abnormalities.[50] Prospective multicenter international CORE320 trial has demonstrated that by measuring simultaneous CCTA and CTP, CT has the potential to assess both anatomy and physiology in a single imaging session.[51] Magalhães *et al*. compared CCTA/CTP against a reference standard of stenosis. They found that combined CCTA/CTP had lower sensitivity, however, specificity and overall accuracy were higher in comparison to CCTA alone.[52] In a recent study, Rief *et al*. compared performance of CTP and CMR with a reference standards of quantitative ICA and MPS or ICA alone. Per-patient diagnostic accuracy, sensitivity, specificity of CTP and CMR were 63% and 75%, 92% and 83%, and 45% and 70%, respectively. It was observed that the diagnostic performance of CTP was similar to CMR.[53]

Another promising technique is the measurement of CT fractional flow reserve (CTFFR). This technique uses computational fluid dynamics to provide a prediction of the invasive FFR. DISCOVER-FLOW trial demonstrated CTFFR has a diagnostic accuracy of 84.3% per vessel, and 87.4% per patient, in comparison with invasive FFR as the gold standard.[54] These promising results were also replicated in DeFACTO and NXT trials.[55,56] The PLATFORM trial used CTFFR as part of a strategy comparing CTCA with standard care. Authors found that CTFFR is a feasible and safe alternative to ICA and is associated with a significantly lower rate of ICA showing no obstructive CAD.[57] Douglas *et al*. found that CTCA led to reduced referrals for ICA and also had similar clinical outcomes at 1 year and lower cost than usual care.[58]

Discussion

It has been appreciated for years that apparent anatomical stenosis severity does not show a linear correlation with its physiological severity. Physiologic severity as defined by coronary pressure and/or flow has resurged into clinical prominence as a potential, fundamental change from anatomical to functional guided management.[5] Boden *et al*. demonstrated that in patients with stable CAD, percutaneous coronary intervention (PCI) did not reduce the risk of death, MI, or other major cardiovascular events when added to optimal medical therapy.[59] DEFER study was one of the first studies to demonstrate the importance of functional assessment of CAD. Authors showed that PCI in lesion with FFR ≥0.75 failed to improve clinical outcomes, i.e., event-free survival, combined cardiac mortality, and MI or percentage free of angina. They even indicated that PCI in Reference group (i.e., FFR <0.75) failed to prevent cardiac death or acute MI, but in fact was associated with a five times incidence of these outcomes compared to medical therapy alone of similar anatomical appearing lesions (~15 vs. ~3%).[60] Hence, there is a very rapidly evolving role of perfusion imaging to determine the functional aspect of CAD. A brief comparison between different modalities has been done in Table 1.

In a recent study by Dey *et al*., patients underwent CCTA and 13-NH3 PET perfusion. They demonstrated that the burden of noncalcified plaque better predicts abnormal MBF than the degree of stenosis. Patients with abnormal MBF were shown to have significantly more noncalcified arterial plaque, low-density noncalcified plaque, and total plaque burden.[61] Assante *et al*. demonstrated that Coronary artery calcium score (CCS) correlates inversely with stress MBF and CFR. It may serve as an independent risk factor for reduction in CFR.[62] In a recent meta-analysis Takx *et al*. compared diagnostic performance of CMR, PET, MPS, CTP, and stress echocardiography in comparison to FFR by ICA. They found that CMR, PET, and CTP are better techniques for diagnosing CAD at both vessel and patient level than MPS and stress echocardiography.[45] These studies have shown that CAD has very complex multifactorial pathogenesis, and its overall impact on the vascular flow is not linear. It may involve major epicardial coronary vessels, small vessels, and endothelium. A complete characterization of the disease process may be become possible by combining PET or MPS with CCTA, CCS, or magnetic resonance imaging (MRI).

As mentioned in Table 1, various imagine modalities have their advantages and disadvantages as well. It is very important to note that few meta-analysis has shown MPS is less sensitive in comparison to PET and CMR. However, there is a wide availability of hybrid MPS/CT cameras and significant advancement in the gamma camera systems.[21-24] Future studies may unveil an improvement in the diagnostic performance of MPS. Diagnostic data on the efficiency of MPI by MPS are enormous, while it is still developing for PET and relatively scarce for CMR, CTP, and CME. MPS is widely available and most extensively validated. PET has the highest diagnostic performance, while CMR

Table 1: Comparison of myocardial perfusion imaging by myocardial contrast echocardiography, myocardial perfusion scintigraphy, positron emission tomography, cardiac magnetic resonance, and computed tomography perfusion

	MCE	MPS	PET	CMR	CTP
Avalability	+	++++	++	++	+
Sensitivity	++	++	++++	+++	++
Specificity	++	++	+++	+++	++
Portability	Yes	No	No	No	No
Cost	++	++	+++	+++	++
FOV	+	+++	+++	+++	+++
Vascular structure	-	-	-	++	+++
Myocardial flow measurement	++	++	+++	++	++
Spatial resolution	+++	+	++	+++	+++
Temporal resolution	+++	+	++	++	+++
Morphological information	++	+	+	+++	++
Cardiac functional information	+++	++	++	+++	+
Tissue characterization	++	+	++	+++	++
Validation	+	++++	++	++	+
Radiation Burden	-	+++	++	-	+++
Limitation	Poor echo, reduced sensitivity in the posterior wall, operator dependency	Prone for artifacts, long procedure time	On-site cyclotron or generator	Metallic implants, Gadolinium allergy, low GFR, Breathhold, Claustrophobia, Dark rim artifact	Arrhythmias, allergy to contrast, renal impairment, breath hold

++++ : most/ best or maximum (as applied), + : least/ lowest/ smallest or minimum (as applied), ++/ +++ : in progressively increasing or decreasing grades, - : Not applicable, MCE: Myocardial contrast echocardiography, PET: Positron emission tomography, CMR: Cardiac magnetic resonance, CTP: Computed tomography perfusion, GFR: Glomerular filtration rate, MPS: Myocardial perfusion single photon emission-computed tomography, FOV: Field of view

provides a similar diagnostic performance as PET without ionizing radiation. CCTA provides excellent resolution of coronary arteries with the potential to measure CTP and CTFFR in single sitting. Overall combined anatomical and perfusion-based noninvasive hybrid imaging offer the potential for best diagnostic accuracy.[24-27] Such an approach would represent a paradigm shift in the era of personalized medicine. Multimodality fusion imaging (MPS/CT, PET/CT, and PET/MRI) would complement each other and have the potential to become gatekeeper in the diagnosis and management of CAD.

Conclusions

MPI gives an insight into the cardiac perfusion, which is often inaccessible by ICA. There is a continuous shift of imaging from mere demonstration of the effect of CAD on blood flow to complete evaluation of perfusion, function, and metabolism. This holds true even for subclinical CAD and in patients with endothelial dysfunction. Functional imaging has "in vivo" holistic capability to image and quantify IHD rather that evaluating only epicardial CAD burden. MPI has proved it is effectiveness in diagnosis, risk stratification, and management of CAD patients. It also influences the management and prognosis of the patients. In summary, a multimodality imaging approach should be able to provide detailed anatomical and functional information in patients suspected of CAD or known CAD. A multimodality hybrid MPI would be the next step in the era of "precision medicine."

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Conflicts of interest

There are no conflicts of interest.

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