Myocardial Perfusion Imaging from Echocardiography to SPECT, PET, CT and MRI – Recent Advances and Applications

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Abstract

This article highlights recent advances in myocardial perfusion imaging in echocardiography, single-photon-emission computed tomography, positron-emission tomography, cardiac computed tomography and cardiac magnetic resonance imaging. The future of non-invasive cardiac imaging is trending towards comprehensive studies combining different modalities to evaluate both cardiac anatomy and its functional status.

Keywords

Myocardial perfusion imaging (MPI), single-photon-emission computed tomography (SPECT), positron-emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), echocardiography, coronary artery disease

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Coronary artery disease (CAD) represents a tremendous financial and health burden as the leading cause of death in the US.[1] Acute coronary syndrome and its subsequent manifestations, including heart failure and need for cardiac transplantation, are associated with significant morbidity and mortality. Hypertension, dyslipidaemia, tobacco abuse, diabetes, chronic kidney disease and family history of CAD are important risk factors for the development and progression of CAD. Sensitive, accurate and reproducible tests to detect CAD are therefore important for risk stratification to optimise patient outcome and contain rapidly escalating medical care costs through pre-morbid diagnosis and treatment.

The development of myocardial ischaemia begins with coronary stenoses, which lead initially to a reduction in perfusion followed by diastolic dysfunction, regional systolic wall motion abnormality, ST-segment depression on electrocardiography (ECG) and, finally, angina – a sequence known as the ischaemic cascade. Detecting disease at its earliest stage will allow for medical intervention and reduce future cardiovascular events. However, atherosclerosis and consequent regional perfusion disparities due to endothelial dysfunction may occur at the microvascular level prior to the development of significant stenoses seen on coronary angiography or wall motion abnormalities on stress echocardiography. Coronary remodelling progresses by outward compensatory expansion of atherosclerosis while preserving the lumen area in minimal and moderate CAD; this is followed by luminal narrowing in severe CAD.[2] Use of coronary intravascular ultrasound has demonstrated outward remodelling of the elastic external membrane of the diseased segment while keeping the luminal area the same as the nearby disease-free segment.[3] In addition, several studies have shown that the majority of myocardial infarctions (MIs) are associated with non-flow-limiting unstable plaques.[4] Delcour et al. showed that patients with normal coronary angiography but abnormal myocardial perfusion imaging (MPI) may predict a higher likelihood of future cardiovascular events.[5] Invasive evaluation of perfusion such as fractional flow reserve (FFR) is associated with peri-procedural complications of infection, bleeding, coronary dissection and stroke. In low- to intermediate-risk populations, the risks may outweigh the benefits of an invasive procedure. Therefore, non-invasive evaluation of myocardial perfusion is preferred in these settings.

Currently, there are many non-invasive techniques of myocardial perfusion, including single-photon-emission computed tomography (SPECT), positron-emission tomography (PET), cardiac magnetic resonance imaging (CMRI), echocardiography and contrast-enhanced multidetector computed tomography (CE-MDCT). These techniques offer robust risk stratification, with a normal study indicating a very high likelihood of cardiac event-free survival.[6–9] Although these techniques were first introduced many years ago, recent advances in contrast materials, stress agents and technical aspects have improved their sensitivity and specificity. This article will outline some of the recent advances and their applications in each imaging modality.

Echocardiography

Stress echocardiography is widely used for diagnosis and risk stratification of CAD. Its relatively low cost, ability for bedside examinations, quick interpretation and high temporal/spatial resolution (0.6–1mm and 15–60msec, respectively)[10] have led to increased utilisation of this technique. However, regional wall motion abnormalities do not become apparent until the disease becomes moderate to severe, as demonstrated by cases of normal stress echo but evidence of ischaemia on MPI. The sensitivity is further reduced in the approximately 10% of patients who are unable to reach target heart rate secondary to chronotropic incompetence or limiting side effects.[11]

Realtime myocardial contrast echocardiography (RTMCE) is an emerging technique capable of rapidly assessing myocardial perfusion at the capillary level using gas-filled microbubbles (<10µm) that are encapsulated with lipid, albumin or biocompatible polymers, thus generating an ultrasound signal to allow visualisation of perfusion.[12,13] These microbubbles are able to traverse the pulmonary capillary circulation and persist within the systemic circulation.[14] The contrast enhancement observed after intravenous injection of microbubbles reflects capillary cross-sectional area. With RTMCE, a high-mechanical-index impulse (flash impulse) can be given to clear the myocardial capillaries of microbubbles (known as the destruction phase). The subsequent rate of contrast replenishment (correlating with flow velocity) and the plateau ultrasound intensity (representing cross-sectional area) can be used to calculate changes in the volume of blood flow. The replenishment kinetics is curvilinear, with the relationship between time (t) and signal intensity (y) expressed to an exponential function of $y = A(1–e^{-\beta t})$, where A is the plateau intensity reflecting blood volume within the systemic capillaries and β is the mean flux rate of blood flow. Relative blood flow can be calculated by the product of blood volume and velocity ($A \times \beta$),[15] which has correlated well with quantitative PET perfusion in humans.[16] With continuous dobutamine and microbubble infusion, echocardiography images are taken before, during and after the flash impulse; areas with abnormal subendocardial replenishment of myocardial contrast represent perfusion defects.[15,17]

In addition to diagnosing ischaemia and evaluating blood flow, RTMCE can be useful in determining the extent of myocardial viability in patients with chronic ischaemic cardiomyopathy with low-dose dobutamine. Viability predicted by RTMCE was shown to correlate well with CMRI.[18] Other studies have shown RTMCE to provide prognostic information regarding left ventricular (LV) function recovery, death and heart failure.[19–22] In a retrospective study of 788 patients undergoing dobutamine RTMCE, the three-year event-free survival rate was 95% for patients with normal myocardial perfusion and wall motion and 82% for those with normal wall motion but abnormal perfusion, suggesting incremental prognostic value of both wall motion and perfusion.[6]

Studies have shown reduced specificity for CAD compared with wall motion,[23,24] mainly due to attenuation of ultrasound beam and lack of standardisation of myocardial contrast echocardiography protocols. However, when these variables are corrected, the higher resolution (≤1mm) seen on echo has been shown to detect perfusion defects not visualised by SPECT imaging (10–11mm).[25,26] Sensitivity to detect CAD with RTMCE in both dobutamine and treadmill exercise ranged between 85 and 99% in a study population of 254 patients.[27]

In October 2007, the US Food and Drug Administration (FDA) issued a black box warning on the echocardiography contrast agents Definity® and Optison® after reports of serious cardiopulmonary reactions within 30 minutes following administration in high-risk patients.[28] However, studies since then have shown that ultrasound contrast agents are not associated with short-term or long-term risk of death or MI.[29,30] Currently, many echocardiography laboratories are still employing the use of echo contrast except for those with severe pulmonary hypertension and known intracardiac shunts.

The advent of realtime 3D echocardiography (RT3DE) technology has provided volumetric imaging and quantification of myocardial perfusion.[31] Iwakura et al. have shown that RT3DE can be used to assess subendocardial perfusion, and that this technique predicts infarct size and functional recovery more precisely than 2D myocardial contrast echocardiography.[32] However, limitations of RT3DE include the need for post-acquisition processing, lower spatial resolution leading to subendocardial artefacts and lack of quantitative measurement using replenishment curves as in 2D myocardial contrast echocardiography. Future advances in technology are needed to resolve these limitations.

Single-photon-emission Computed Tomography

SPECT is a widely available nuclear technique to assess myocardial perfusion using radiotracers such as thallium-201 (Tl-201) or technetium-99m (Tc-99m). Images of regional myocardial blood flow (MBF) are obtained at rest and during stress. In the presence of significant coronary artery stenosis, heterogeneous myocardial perfusion occurs when comparing rest with stress, and the difference is detected by SPECT. Although SPECT is very sensitive, it has suffered from limitations including long image acquisition, low image resolution, reduced specificity due to soft-tissue attenuation and use of radioactive material. Recent advances in image reconstruction, detector crystals, new vasodilator agents, new hardware and incorporation of other imaging modalities have aimed to increase sensitivity or reduce patient side effects while maintaining image resolution and decreasing acquisition time.

Image Reconstruction

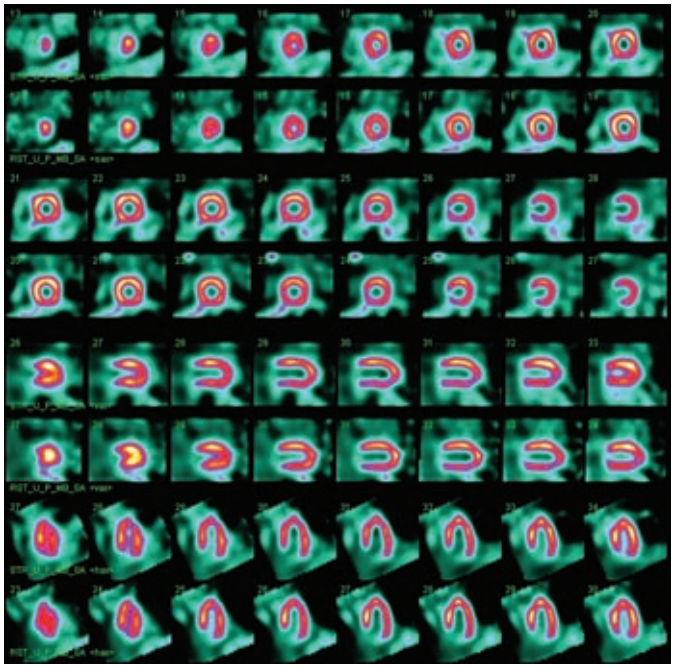
Current myocardial perfusion SPECT (MPS) is performed by standard dual-head scintillation cameras with collimators in 90º detector geometry and image reconstruction based on a standard filtered-back projection (FBP) algorithm, which back-projects 2D images into a virtual 3D space. However, FBP requires longer scanning time, is susceptible to motion artefacts, and has lower resolution due to increased noise. For example, wide-beam reconstruction (WBR) by UltraSPECT uses iterative image reconstruction that enables simultaneous resolution and contrast recovery combined with improved signal-to-noise ratio. WBR requires much less data input compared with FBP and can achieve similar-quality images by using half-projection at 6º, half the radiation dose or half the acquisition time. This technique has been compared with FBP by Borges-Neto et al. and other groups, who have shown highly significant correlations between variables including LV ejection fraction (LVEF), end-systolic and -diastolic volumes, summed rest score (SRS), summed stress score (SSS) and summed difference score (SDS).[33,34]

Detector Crystals

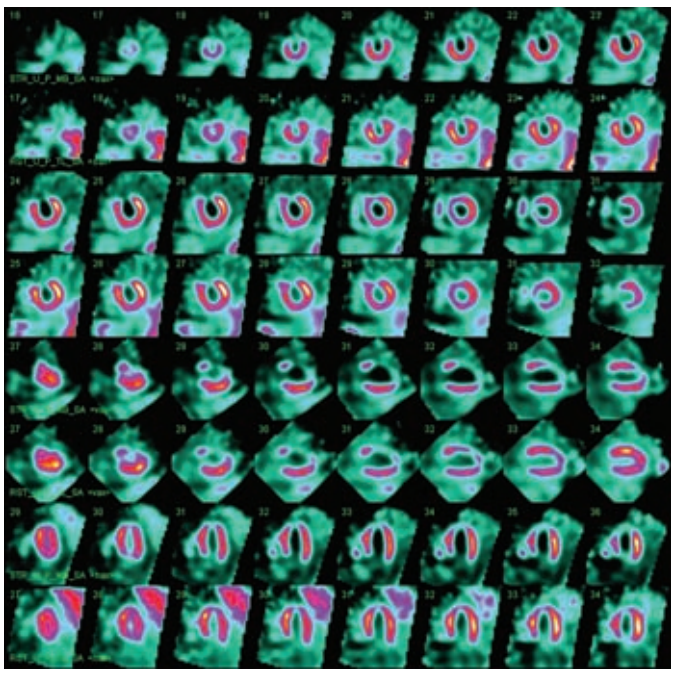
Detector crystals in SPECT convert gamma-ray photons into electrical signals, which are then used to form 3D images from multiple projections. Image quality is dependent on the properties of these detectors. Desired detectors have high intrinsic efficiency, energy and spatial resolution.[35] Traditionally, sodium iodide crystals doped with thallium, NaI(Tl), have been used in most SPECT systems. However, other detector crystals are in development due to NaI(Tl)'s low spatial and energy resolution.

Cadmium zinc telluride (CZT) is an alloy of cadmium telluride and zinc telluride that was incorporated into the SPECT system due to its high atomic number, leading to higher detector efficiency compared with NaI(Tl). Other detector crystals in development include cadmium telluride (CdTe), silicon strip detector, charge-coupled

Figure 1: Tc-99m Tetrofosmin Single-photon-emission Computed Tomography Myocardial Perfusion Imaging



A: Stress (top) and rest (bottom). Shown in paired rows. Images were obtained with the cadmium zinc telluride (CZT) detector and iterative reconstruction, shown in the short axis (apex to base from upper left to mid-right), vertical long axis (septum on the left) and horizontal long axis (inferior on the left). These images were obtained in six minutes at rest and four minutes with stress. A mild septal ischaemia is demonstrated.



B: Stress (top) and rest (bottom). These images demonstrate a large severe minimally reversible (predominantly fixed) anterior defect with minimal reversible ischaemia in the septal and anterolateral segments.

device, sodium-activated cesium iodide and thallium-activated cesium iodide CsI(Tl). However, further research is needed to validate these detectors.

Vasodilator Agents

The commonly used pharmacological radionuclide stress perfusion agents are adenosine, dipyridamole and dobutamine. Adenosine and dipyridamole are coronary vasodilators, whereas dobutamine is a beta-agonist that increases heart rate and myocardial contractility, with similar effects to physiological exercise. Vasodilators with adenosine and dipyridamole account for 44% of stress perfusion studies performed annually in the US.[36] However, both adenosine and dipyridamole can have minor and major side effects due to non-selective stimulation of all four subtypes of adenosine receptor: A_1 leads to renal vasoconstriction and atrioventricular (AV) nodal conduction block, A_{2A} leads to sympathetic surge and coronary vasodilation and A_{2B} and A_3 lead to bronchoconstriction.[37] The selective A_{2A} receptor agonist regadenoson has been demonstrated to rapidly increase coronary blood flow, yet selectively does not cause AV nodal block and bronchospasm.[38,39] Regadenoson has also been shown to have a better side-effect profile, to be safely administered and to be sensitive in the detection of myocardial ischaemia regardless of age, gender, body habitus or diabetes.[40,41] Currently, regadenoson is commercially available and used in many nuclear cardiology laboratories. Binodenoson, another A_{2A} receptor agonist, has been shown to have similar extent and severity of reversible perfusion defects on SPECT imaging, with fewer side effects.[42] One other agent within the same class, apadenoson, is in phase III trials and may become available in the near future.

New Hardware

Dedicated hardware camera systems have been introduced to optimise acquisition geometry and tomographic sampling. The Cardius XPO camera by Digirad, Inc. uses a two- or three-detector configuration and a CsI (Tl) detector to create a more compact system than used in conventional cameras.[43] This has resulted in a reported 38% reduction in acquisition time.[44] D-SPECT by Spectrum Dynamics uses nine collimated and pixelated CZT detector arrays that are placed in 90º geometry to acquire data focusing on a cardiac region of interest. This system is able to achieve an acquisition time as short as two minutes, with higher sensitivity and better energy resolution than conventional SPECT (see *Figure 1*).[45]

Other Imaging Modalities

Computer-generated valve planes in MPS can be misaligned with the true valve plane, leading to inaccurate analysis of myocardial perfusion. In a retrospective study, Slomka et al. demonstrated improved quantitative MPS analysis by software co-registration of both CT angiography (CTA) and MPS, thus allowing for CTA-guided contour and vascular territory adjustments. This technique results in a success rate of 96% as assessed visually and improved area under the receiver operating characteristic (ROC) curve for detection of CAD.[46] Combining SPECT and CT suggests that the use of hybrid imaging provides added diagnostic value; however, the clinical impact on treatment strategy and patient outcome remains to be determined in prospective studies.

Positron-emission Tomography

PET has long been the gold standard of MPI and quantitation. The most commonly used perfusion tracers for PET are nitrogen-13 (N-13), ammonia, rubidium-82 (Rb-82) and oxygen-15 (O-15) water, with Rb-82 being the most common in the US as it is non-cyclotron-generated and is available to most laboratories.[47] Compared with other perfusion imaging techniques, PET offers many advantages, including higher spatial and contrast resolution, improved image quality, accurate attenuation correction, higher diagnostic accuracy and excellent risk stratification.[47] A meta-analysis of studies

between 1997 and 2007 by Nandalur showed the sensitivity and specificity of PET as a diagnostic test for CAD to be 92 and 85%, respectively.[48] Other studies have compared PET and SPECT head to head with PET, showing higher sensitivity and specificity and reduced attenuation artefacts with PET.[49] Sampson et al. also demonstrated high diagnostic accuracy with PET/CT hybrid imaging.[50] In addition, PET can assess wall motion at peak hyperaemia, and the LVEF reserve can be used to exclude left main or three-vessel CAD non-invasively.[51] Risk stratification with PET perfusion imaging has emerged as a useful tool. Yoshinaga et al. have shown increased cardiac annual event rates in those with higher SSS and low LVEF. The annual hard event rate was 0.4, 2.3 and 7.0% in the normal, mild and moderate to severe groups, respectively.[7] Other advantages of PET include the ability to quantify MBF to diagnose coronary microvascular dysfunction.[52] Lastly, PET imaging can be used to assess myocardial viability by using ^{18}F-fluorodeoxyglucose (FDG) to determine areas of myocardium capable of glucose metabolism, thus directing the need for revascularisation. Combined with PET perfusion imaging, D'Egidio et al. have shown that in patients with LVEF <35% and CAD who are being considered for revascularisation, revascularisation is superior to medical therapy in terms of cardiac death, MI and cardiac repeat hospital stay at one year when the mismatch between perfusion defect and FDG defect is >7%.[53]

Cardiac Magnetic Resonance Perfusion Imaging

CMRI has the ability to assess MBF non-invasively and without radiation exposure by recording signal intensity over time characteristics of gadolinium, a paramagnetic contrast agent that shortens T_1 (longitudinal relaxation time reflecting the rate at which the tissue's proton alignment recovers after application of radiofrequency pulse). First-pass imaging using CMRI was developed in 1990 for evaluation of perfusion in which images are acquired in pre-selected planes or slices as gadolinium traverses the vasculature and into the myocardium.[54] The bright signal generated and the rate of signal increase reflects MBF.[55] Use of techniques such as parallel imaging[56] allows multiple slices of data to be obtained through one pass of gadolinium. Additionally, endocardial artefacts can be minimised with improvement in temporal resolution.[57] It has been shown that CMRI can differentiate haemodynamically relevant and non-relevant coronary stenoses better than invasive angiography and FFR.[58,59] Others have suggested that CMRI may be sensitive enough to detect 50% coronary stenoses by quantifying myocardial flow reserve.[60] A recent multicentre trial suggested that CMRI is a valuable alternative to SPECT for detecting CAD.[61] With the use of late gadolinium enhancement infarction imaging, the diagnostic performance of CMRI can be improved.[62] CMRI has been shown to have sensitivity of 88%, specificity of 90% and accuracy of 89%.[63] More importantly, prognostic studies with stress CMRI are consistent with the established literature for SPECT and PET in predicting cardiac events.[9,64]

Conventional CMRI uses a 1.5 Tesla (1.5T) magnet; however, images can be suboptimal due to the need for rapid acquisition. It has been suggested that contrast enhancement in CMRI can be improved using a stronger magnet at 3T, which results in improved image quality.[65] In pig models using labelled microspheres as the gold standard for MBF, Christian et al. recently showed that measurement of absolute MBF with first-pass CMRI is accurate at both 1.5T and 3T (3T: r=0.98, p<0.0001; 1.5T: r=0.95, p<0.0001). However, signal quality is better at 3T, with a narrower 95% confidence interval.[66]

With the increase in popularity and application of CMRI, the potential complication of nephrogenic systemic fibrosis (NSF) with the use of gadolinium in patients with advanced kidney disease must be considered. NSF (first identified in 1997; first published report of 14 cases in 2000)[67] is a highly debilitating and potentially life-threatening condition characterised by progressive fibrosis involving the skin, pleura, lungs, joints, pericardium and muscle.[68] NSF has only been described in patients on dialysis or with a glomerular filtration rate (GFR) <15ml/min/1.73m^2;[69] therefore, the use of gadolinium should be avoided in patients with a GFR <30ml/min/1.73m^2, regardless of age, race or sex.[70]

Perfusion imaging with CMRI can be achieved without the use of exogenous contrast agents. Using water as a freely diffusible tracer and a technique called arterial spin labelling (ASL), blood flowing into a desired image slice is magnetically labelled. As the blood exchanges with tissue water and thereby changes tissue magnetisation, a change in signal is detected and a perfusion map can be calculated.[71] Quantification of MBF using ASL has been shown to be possible in rabbits.[72] When combined with vasodilator stress testing in humans, it is possible to show a lower perfusion reserve in areas with coronary stenosis.[73,74] However, an important limitation of ASL is that a large increase in MBF results in a relatively small increase of signal, thereby reducing its sensitivity compared with gadolinium-based CMRI.

Cardiac Computed Tomography

Initial cardiac CT with ECG gating used electron-beam CT (EBCT) to calculate the calcium score of coronary arteries to stratify the risk for coronary atherosclerosis.[75] However, EBCT does not provide ventricular functional information such as can be obtained with other imaging modalities. Contrast-enhanced multidetector computed tomography (CE-MDCT) is an emerging technology that examines myocardial perfusion. Using first-pass imaging (adenosine-augmented CE-MDCT), George et al. were able to demonstrate coronary flow deficit during adenosine stress in a canine model. The regional myocardial signal density showed a linear relationship compared with microsphere-derived MBF up to 8ml/g/minute.[76] Furthermore, subendocardial hypoperfusion at systole and normal perfusion at diastole seen in CE-MDCT has been suggested to be characteristic of ischaemic myocardium.[77] Volumetric quantification of myocardial perfusion using 3D data sets from MDCT allows for accurate detection of perfusion defects compared with MPS.[78] Recently, Okada et al. showed comparable detection, extent and severity of perfusion defects at rest and during stress between CT perfusion (CTP) and SPECT.[79] In addition to CTP, a comprehensive study with CTA for visualisation of coronary anatomy and CT delayed enhancement to evaluate for infarction and necrosis (similar to late gadolinium enhancement in CMRI)[80] can be obtained as a second scan a few minutes later, with a similar total radiation dose to SPECT.[81] While there have been studies on the prognostic value of CTA,[82–86] the prognostic value and diagnostic accuracy of CTP are unclear, despite recent advances. Future clinical trials are needed for risk stratification to optimise patient outcome.

Summary

The recent advances and developments in MPI provide clinicians with multimodality tools for evaluating patients with suspected

or known CAD. However, a comprehensive assessment of CAD should include both coronary anatomy and its haemodynamic significance. Combination of different non-invasive imaging techniques has been shown to have excellent accuracy in detecting flow-limiting stenoses compared with invasive approaches, and this type of 'hybrid' imaging may serve as a gatekeeper prior to revascularisation.[82,87] With this in mind, the future of non-invasive imaging may very well head towards a multidisciplinary approach involving cardiology, nuclear medicine and radiology in order to optimise patient care. ■

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