STATE-OF-THE-ART REVIEW

Imaging techniques and coronary artery disease – a review

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Abstract
In this paper, the most widely used and extensively validated techniques for imaging coronary artery disease are reviewed. We describe and compare the roles of echocardiography, cardiac nuclear imaging techniques and cardiac magnetic resonance imaging.

For now we see through a glass, darkly.

Echocardiographic imaging

Two-dimensional evaluation of coronary artery disease at rest
Evaluation of left ventricular (LV) systolic function and wall motion at rest remains the cornerstone of diagnosis of coronary artery disease (CAD). Transthoracic echocardiography not only allows the detection of coronary territories affected after a myocardial infarction, but also visualizes the complications and functional consequences of CAD. In addition, echocardiography is the first step in the evaluation of myocardial viability and is closely correlated with prognosis.

Wall motion analysis and wall motion score index
Ischaemia can be visualized by echocardiography when flow-limiting stenosis or acute obstruction of a coronary artery is severe enough to disturb wall motion at rest. Both the diastolic and systolic function of the jeopardized territory are affected in acute ischaemia, even before the electrocardiographic manifestations of ischaemia become apparent. A main limitation of echocardiographic wall motion evaluation is the qualitative nature of analysis, which increases disagreement between observers. Segmental analysis of wall motion could be mapped on a 16- and 17-segment model to decrease subjectivity of the test. Wall motion score index (WMSI) is a reflection of global LV contractility and is calculated by scoring individual segments of the left ventricle and then dividing the sum by 16 or 17. WMSI closely correlates with ejection fraction (EF) measured using echocardiography or other imaging modalities.1 After an acute myocardial infarction (AMI), the prognostic power of WMSI at rest is higher than that of EF.2 However, WMSI is also limited by subjectivity, because the assessment of wall motion is observer dependent.

Limitations of transthoracic imaging for the evaluation of coronary artery disease
Echocardiographic imaging is particularly useful when motility of the underlying CAD is sufficient to cause segmental wall motion anomaly at rest. This can be observed in patients with an acute coronary obstruction or in those with critical CAD that prohibits myocardial nourishment, even at rest. A stress modality is usually needed to evoke wall motion anomaly in patients with less severe CAD. A variety of stressors can be used, such as exercise or pharmacological agents, which are detailed below. Echocardiographic evaluation of wall motion is prone to errors because of effects such as translational motion of the heart and tethering of the infarcted area. Observation of wall thickening is less prone to such technical caveats than observation of endothelial excursion alone. In addition, the

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segment of interest can shift from the observed plane during systolic and diastolic motion of heart as a result of the two-dimensional (2D) nature of conventional echocardiography. This problem is especially important during deformation imaging. Three-dimensional (3D) echocardiography could help to alleviate this problem, although the resolution of 3D transoesophageal echocardiography (3D TTE) is still low.

Echocardiographic measurement of coronary flow reserve

Coronary flow reserve (CFR) is the ratio of maximal blood flow to baseline blood flow in a given artery. Although initially measured angiographically, improvements in echocardiographic image quality have allowed measurement of CFR by transthoracic echocardiography. Distal flow in of three epicardial arteries can be sampled with pulsed-wave Doppler echocardiography. The addition of a contrast agent is imperative if all coronary arteries cannot be visualized. For image acquisition, a high-frequency probe (5–7 MHz) setting is used, along with a sample size of 3–4 ml. Adenosine and high-dose dipyridamole are the agents most frequently used to induce hyperaemia. As these agents are also used in stress echocardiography, an interesting concept is the measurement of CFR in addition to wall motion assessment, thereby allowing a combined approach. A ratio of < 2 indicates compromised flow reserve and is compatible with a functionally significant coronary stenosis. Echocardiographic measurement of CFR has an excellent correlation with catheter-based measurements. In addition to epicardial coronary stenosis, CFR measurements are affected in conditions associated with altered flow at the level of coronary microcirculation, such as myocardial hypertrophy, ageing and changes in myocardial oxygen demand. Coronary flow reserve measurements allow evaluation of functional severity of an intermediate-grade stenosis and detect restenosis or bypass graft occlusion in a previously revascularized segment. In addition, echocardiographic CFR measurements have prognostic implications for chronic CAD, especially when reduced CFR is present in the territory of the left anterior descending (LAD) artery.

Deformation imaging

Deformation imaging, more commonly known as strain ($\varepsilon$) and strain rate ($\varepsilon'$) measurement, is a novel method for analysing LV wall motion. Strain can be defined as per cent change in distance between two points (equation 1).

$$\varepsilon = \frac{\Delta L}{L}$$

(1)

When this formula is applied to LV, $\varepsilon$ defines amount of change between two points on the LV at systole. The temporal rate of this change is termed strain rate (equation 2).

$$\varepsilon' = \frac{\varepsilon}{\Delta t}$$

(2)

Strain and strain rate of the LV should be measured in systole over three different cardiac cycles. Longitudinal strain is measured from apical views and is related to longitudinal movements of the LV. Circumferential strain is the horizontal shortening of the LV, while radial strain encompasses inward motion. Both longitudinal and circumferential strain have negative values in a normally contracting heart, because the final distance between two points in the LV is shorter than the initial distance. In contrast, radial strain has a positive value owing to inward thickening of the myocardium. Strain can be expressed as peak systolic strain per segment, or global average of strain can be used as a surrogate marker of systolic function.

Measurement of strain and strain rate

Echocardiographic measurement of strain and strain rate could be accomplished using tissue Doppler imaging (TDI), by measuring the speed of two regions of interest relative to each other. This measurement would principally allow calculation of strain rate because TDI measures velocity of the tissue and then strain could be derived from $\varepsilon'$. Tissue Doppler imaging allows calculation of longitudinal and radial deformation, but not circumferential strain or myocardial torsion. To obtain the best results, a parallel alignment of the Doppler beam to the systolic motion of the interested region is required.

Speckle tracking

If tissue material has an inhomogeneous distribution, the ultrasound beams cannot fully penetrate the myocardium, resulting in speckle patterns on the echocardiographic image. These speckles have a unique pattern at each region of interest and can be tracked through systole and diastole using a computer algorithm. Thus, quantitative shortening of the myocardium can be tracked from 2D images,
allowing calculation of $\varepsilon$ and $\varepsilon'$. Speckle tracking is not bound by the limitations of TDI, such as angle dependency. This allows measurement of circumferential strain and rotational movements of the myocardium. In addition, myocardial tracking is performed semiautomatically, thus allowing a more practical approach and better inter- and intraobserver variability.\cite{7} To obtain an accurate tracking, frame rates of more than 50–60 frames per second (fps) should be used and at least three cardiac cycles should be recorded with a good image quality.\cite{8,9}

**Diagnosis of coronary artery disease**

Areas of reduced blood flow demonstrate impaired strain and strain rate measurements on both a segmental and global level (Figures 1 and 2). Shimoni et al.\cite{10} found reduced global and segmental longitudinal strain measurements in patients with proven obstructive coronary disease. Global longitudinal strain had a high sensitivity and specificity for diagnosis of obstructive CAD in patients with LV systolic dysfunction at rest.\cite{11} Patients with a higher degree of coronary artery stenosis had higher longitudinal and circumferential strain and lower radial strain than patients with less severe stenosis.\cite{12} Patients with high-risk CAD anatomy (three-vessel or left main CAD) had reduced peak systolic longitudinal strain values compared with patients with one- or two-vessel disease.\cite{13} Deformation imaging could also be useful in detecting subclinical CAD or atherosclerosis. In a study involving 123 patients, Montgomery et al.\cite{14} found significantly lower global longitudinal strain values in patients without objective evidence of ischaemia but significant (> 50%) coronary artery stenosis.

Deformation imaging could be used as an adjunct to stress echocardiography to enhance the diagnostic capability of visual assessment, or as an alternative (Figure 3). Longitudinal and circumferential strain, as measured with 2D speckle tracking, are significantly lower in patients with three-vessel disease than in control subjects on dobutamine stress echocardiography (DSE).\cite{15} Interestingly, in that study, strain measurements were altered at intermediate dobutamine doses, whereas visual assessment of wall movements was still normal. TDI strain, speckle tracking and WMSI were found to have a similar accuracy for detecting CAD.\cite{16} Both circumferential and longitudinal strain had a high sensitivity and specificity for detecting CAD at rest and during DSE, whereas radial strain was less accurate.\cite{17} In contrast, Celutkiene et al.\cite{18} found that

![ FIGURE 1](image1.png) **FIGURE 1** Longitudinal strain measurements obtained with 2D speckle tracking echocardiography in a patient. Note increased strain values at apicolateral, apicoseptal, mid-anteroseptal and basal anteroseptal walls, with post-systolic contraction at mid- and basal anteroseptum. The patient had experienced an acute anterior wall infarction with a subtotal occlusion at mid-left anterior descending artery.
conventional assessment was significantly more accurate than strain parameters for detecting CAD in a series of 151 patients. However, their definition of CAD could be a reason for this result (CAD present in > 70% of at least one coronary artery on coronary angiography) as strain, strain rate and associated measures had higher sensitivity to detect subclinical CAD than WMSI. Exercise is also used as a stressor in combination with deformation imaging. In a study in 16 patients who were scheduled to undergo percutaneous revascularization, peak exercise strain was significantly elevated after target vessel revascularization at jeopardized myocardial segments. Time to peak strain, a marker of post-systolic shortening, was measured 5 minutes after peak exercise and was accurate in detecting significant CAD with a sensitivity of 93% and specificity of 73%.

Assessment of myocardial viability

Deformation imaging can be used to assess viability of the myocardium, and both resting images and stress echocardiography can be used for this purpose. Peak strain measurements taken at rest can accurately evaluate recovery after an AMI. Transmural strain profile, as assessed with TDI and combined with peak systolic strain, allowed identification of non-viable segments with a sensitivity of 100% and specificity.
of 96.6% in 36 ST-elevation myocardial infarction (STEMI) patients. A global longitudinal strain of more than –13.7% after an AMI predicted recovery with high accuracy. In a study of speckle tracking echocardiography combined with adenosine stress, change in peak longitudinal strain of more than 14.6% had a sensitivity of 86.7% and a specificity of 90.2% for identification of viable segments after a myocardial infarction. The sensitivity of low-dose DSE with measurement of longitudinal strain and strain rate was similar to that of single-photon emission computed tomography (SPECT) (89.8% vs. 83.6%), while the specificity was higher (90.2% vs. 74.4%) for the identification of viable myocardium after an AMI.

Other deformation parameters used for diagnosis and evaluation of coronary artery disease

A number of data obtained from TDI strain or 2D speckle tracking are valuable for the diagnosis of CAD. Shortening of myocardial segments after the closure of an aortic valve is indicative of myocardial ischaemia. In normal myocardium, the subendocardial region has higher strain measurements than mid- or subepicardial myocardium. Loss of this strain gradient is a marker of cardiac ischaemia. Myocardial ischaemia affects the diastolic relaxation of myocardial segments prior to systolic dysfunction. Impaired relaxation of myocardial segments at rest has been shown to be a marker of ischaemia, even when peak systolic strain is normal. Detailed explanation of these parameters is beyond the scope of this review and can be found elsewhere.

Stress echocardiography

Critical ischaemia of myocardial segments causes a cascade of changes in myocardial physiology, including disturbances in systolic and diastolic function. Forty years after the pioneering study of Tennant and Wiggers, echocardiographic methods allowed demonstration of wall motion abnormalities during acute ischaemia and infarction in experimental in vivo models. Various stress methods could be used to evoke critical ischaemia, which in turn could be detected by echocardiographic examination of segmental or global kinesis. Wall motion analysis (WMA) is the most frequently employed method for detection of myocardial ishaemia; however, quantitative analysis of myocardial motion or a combination of segmental analysis with myocardial perfusion (with echocardiographic contrast) could be used additionally. As ischaemia disturbs diastolic relaxation of the left ventricle before systolic wall motion abnormalities appear, some researchers have suggested that evaluation of stress-induced diastolic dysfunction of the LV (mitral inflow patterns) or individual segments (deformation analysis) could be used as a surrogate marker of early ischaemia.

Stress methods for echocardiographic analysis

Exercise stress Exercise is the stress method most widely used to induce ischaemia. In patients with adequate exercise capacity, exercise stress echocardiography (ESE) allows measurement of various physiological variables in addition to echocardiographic imaging. In addition, it is suggested that exercise represents a more physiological way of inducing ischaemia, and could correlate better with the symptoms of patients. Treadmill testing or a bicycle ergometer could be used as ischaemic stressors. Treadmill protocols have the advantage of familiarity and standardized protocols. However, obtaining images during peak exercise is difficult because of the position of patients. Image acquisition is limited to end-exercise, when a delay of at least 1 minute can be expected. A bicycle ergometer in the supine position allows acquisition of images during testing; however, stress protocols are less standardized between centres and are unfamiliar to the majority of patients. Some researchers advocate using handgrip tests as the main stressor to induce ischaemia; however, handgrip is usually used as an adjunct to pharmacological stress. Adequate stress is defined as 85% of maximal heart rate, adjusted for age.

Pharmacological stress Pharmacological stress could be used as an alternative to exercise stress in those without adequate exercise capacity, for example elderly and incapacitated patients. However, the use of pharmacological stress is more widespread than appreciated, as some laboratories (especially those located in Europe) prefer pharmacological stress to exercise stress because image acquisition and quality is considerably increased as the patient does not move during echocardiographic examination. Dobutamine is the preferred agent to induce stress as it closely simulates exercise-related changes. Most laboratories use a graded protocol beginning with an infusion rate of 5 μg/kg/min and doubling the dose at 3- to 5-minute intervals. Additional induction of tachycardia can be achieved with...
atropine (1–2 mg) or handgrip stress if the heart rate response is inadequate after 40 µg/kg/min dobutamine. Beta-blockers can be used to neutralize the effects of dobutamine after resting images are acquired. Vasodilators, namely adenosine (with an infusion rate of 140 µg/kg/min over 6 minutes) or dipyridamole (with an infusion rate of 0.84 mg/kg over 6–10 minutes), could be used as an alternative to dobutamine stress. The specificity of vasodilators for the detection of lesions is remarkably good at > 60%, while sensitivity is considerably lower than that of dobutamine, especially when one-vessel disease is present. The addition of atropine to both agents considerably increases sensitivity. A 50-µg intravenous (i.v.) bolus at 5-minute intervals is used up to a total dose of 350 µg. Use of vasospastici agents in a non-invasive setting is worrying for most echocardiographers until the safety of this protocol is proven. Ergonovine stress echocardiography is used to provoke vasospasm in coronary arteries. A 50-µg intravenous (i.v.) bolus at 5-minute intervals is used up to a total dose of 350 µg. Use of vasospastic agents in a non-invasive setting is worrying for most echocardiographers until the safety of this protocol is proven. Intravenous nitroglycerine bolus and sublingual nifedipine are recommended to neutralize the effects of ergonovine.

Other stressors Other stressors that could be combined with echocardiographic imaging include atrial pacing (the transoesophageal approach) and vasoconstrictors (ergonovine; also known as ergometrine). Pacing stress echocardiography has a better safety profile than and a similar accuracy as DSE, but its invasive nature limits its use. Ergonovine stress echocardiography is used to provoke vasospasm in coronary arteries. A 50-µg intravenous (i.v.) bolus at 5-minute intervals is used up to a total dose of 350 µg. Use of vasospastic agents in a non-invasive setting is worrying for most echocardiographers until the safety of this protocol is proven. Intravenous nitroglycerine bolus and sublingual nifedipine are recommended to neutralize early and late effects of ergonovine.

Image acquisition Standard echocardiographic images during stress echocardiography should allow a detailed assessment of all ventricular segments. Commonly used views include parasternal four- and two-chamber views and the parasternal long-axis window and short-axis window views. The parasternal long-axis window view is sometimes replaced by the apical long-axis view, especially when longitudinal strain measurements are desirable. High-quality images with clear delineation of the endocardial border are highly desirable to evaluate endocardial excursion and/or wall thickening. If speckle tracking will be added to standard evaluation, at least three cycles with a minimum frame rate of 50 fps should be recorded from all windows. A vasodilating agent could improve image acquisition, as high-quality images are difficult to obtain at high heart rates. Acquisition of images should be performed at each stage, while echocardiographic monitoring should be continuous during testing. Continuous electrocardiographic recording during echocardiography is crucial to determine ST segment changes and arrhythmias. Ideally, a 12-lead electrocardiogram should be obtained at each stage. Blood pressure is measured with an external cuff at rest and at the beginning of each stage.

Image evaluation A standardized approach would be suitable to increase reliability of the test and facilitate diagnosis. Evaluation of all LV segments should be possible from the recorded images. In general, segments with normal kinesis should remain normal or hyperkinetic during stress and recovery. Visual estimation of kinesia involves observation of systolic endocardial excursion and wall thickness. Systolic excursion is easier to evaluate but could underestimate, or overestimate, wall motion owing to translational movement of heart. Systolic thickening of wall segments is much more specific, but is more difficult to observe, especially when echogenicity is poor. Development of hypokinesia (arbitrarily defined as less than 5 mm of systolic excursion or less than 30% thickening of the LV wall) is indicative of ischaemia in a segment with normal systolic dynamics at rest. As the pattern of hypokinesia follows the location of coronary artery lesions, mapping of hypokinetic or kinetic segments is a useful approach to detect which coronary artery segments are stenotic (Figure 4). For this purpose the LV is divided into 16 or 17 segments, and kinesis of each individual segment is evaluated with a scoring system (Figure 5). The sum of all scores divided by the total segments observed gives the wall motion score (WMS). Any score above 1 is abnormal and indicates segmental anomalies caused by ischaemia or an associated condition.

In addition to new wall motion defects, a few other responses can be observed during stress testing. Development of kinesia in a previously hypokinetic segment indicates non-viable myocardium. In contrast, normalization of systolic contraction in a previously hypokinetic segment indicates viable tissue, especially when the observation was made during low-dose dobutamine infusion (< 10 µg/kg/min). Some authors suggest that normokinesis during peak exercise or maximal
dobutamine dose indicates ischaemia, as the normal response should be hyperkinesis; however, this notion is not accepted by all echocardiographers. Regional normokinesis is more probably related to ischaemia when other LV segments are hyperkinetic. In addition to visual estimation, other techniques for quantification of regional motility are available. Deformation imaging during stress echocardiography is discussed below.

### Diagnostic accuracy of stress echocardiography

Both exercise (treadmill and bicycle ergometer) stress and DSE have good accuracy for the detection of CAD when coronary angiography is used as gold standard. The sensitivity of stress echocardiography is between 71% and 94% on average. A meta-analysis found that DSE had a sensitivity of 80%, while the specificity was 84%, and the latter was found superior to dobutamine SPECT study. Dipyridamole had superior specificity for CAD than ESE, DSE or dipyridamole SPECT, although the sensitivity is lower, especially for one-vessel disease. The specificity of DSE can be enhanced by using high-dose protocols or by

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**FIGURE 4** Calculation of wall motion segment index with DSE. All segments are observed at baseline, during low-dose dobutamine infusion, at peak heart rate and at recovery. A number between 1 and 5 (sometimes between 1 and 7) is assigned to each individual segment on apical four-chamber, apical two-chamber, parasternal long-axis and parasternal short-axis views. Wall motion score index is then calculated by dividing the sum of all segments by 16 (or 17). In this example, the baseline motion of all segments was normal. The apical long-axis view is replaced by the parasternal long-axis view to calculate longitudinal strain.

**FIGURE 5** Bull’s-eye representation of all segments (top) and WMS (bottom). One point is given to segments with normal contractility. Wall motion score is increased as the motility of the observed segment is reduced. Five points are given to segments with aneurysmal dilatation. In this example, further scoring is given according to the presence of scar tissue.
the addition of atropine. Therefore, it is prudent to make the choice of stressor according to patient and laboratory characteristics, such as choosing exercise over pharmacological stress when additional physiological output is valuable for decision-making or using dobutamine instead of dipyridamole when the patient has asthma. It should also be noted that these figures assume that the test is performed by adequately trained personnel, and necessary training in echocardiography should be undertaken before attempting a stress echocardiography examination.

Assessment of viability

Myocardial viability is an important concept for evaluation for potential revascularization, as there are many studies demonstrating reduced benefit for surgical or percutaneous revascularization when the myocardium supplied by stenotic vessel is no longer viable. In contrast, both ventricular systolic function and prognosis improve when a large myocardial region is viable and jeopardized.

To determine viability, low-dose dobutamine, low-dose dipyridamole, adenosine, enoximone and low-intensity exercise could be employed. Low-dose dobutamine is the drug most frequently used in stress echocardiography to determine viable tissue. In a myocardial region with hypokinesis, no improvement in contractility with dobutamine identifies non-viable areas that will not be improved after revascularization. Increased contractility with low-dose (< 10 µg/kg/min) dobutamine strongly suggests that improvement will be achieved after restoration of blood flow; this response is even more significant if contractility is reduced at higher doses (biphasic response). In contrast, increased contractility with high-dose dobutamine does not identify regions that will be improved after revascularization.

Dobutamine stress echocardiography has good specificity for recovery of regional function after revascularization, but the sensitivity of DSE is lower than that of thallium-201 (201Tl) or 18-fluorodeoxyglucose (18-FDG) positron emission tomography (PET). In a study conducted by Korosoglou et al., DSE had a sensitivity of 83% and a specificity of 76% for viability. The presence of four or more viable segments as detected with DSE predicts improved EF and New York Heart Association (NYHA) class after revascularization in patients with ischaemic cardiomyopathy. Dobutamine stress echocardiography agrees with 201Tl SPECT (89%; \( P < 0.001 \)) and dual-isotope simultaneous acquisition (DISA) -SPECT (81%; \( \kappa = 0.46 \)) for recovery after revascularization. In their study, Yasugi et al. found a negative predictive value (NPV) and positive predictive value (PPV) for DSE of 90% and 79%, respectively.

Prognostic implications in coronary artery disease

A positive stress echocardiographic study identifies patients at high risk of acute coronary events and mortality, regardless of stress modality. In contrast, a negative study identifies patients with a low probability of future cardiac events. However, a maximal test should be carried out for prognostic assessment. A trend towards higher all-cause mortality with a normal submaximal stress echographic study compared with normal maximal stress echographic study was observed in a meta-analysis [relative risk (RR 1.36); \( P = 0.15 \)].

Contrast echocardiography

Contrast echocardiography can be used to identify intracardiac shunts, to augment Doppler signals, to enhance endocardial borders and to assess myocardial perfusion. Enhancing the borders and assessing perfusion [myocardial contrast echocardiography (MCE)] are important in the evaluation of CAD. Improving the endocardial border delineation with contrast imaging, which provides detailed WMA, is especially important in patients in whom adequate imaging is difficult or suboptimal for a variety of reasons (e.g. obesity, thorax deformity and lung disease). It is also possible to assess myocardial microcirculation, and hence perfusion, with the new ultrasound and microbubble technology. However, training is needed to ensure accurate interpretation and it is important to use contrast-specific imaging modalities when contrast agents are used.

Global/regional wall motion assessment and stress echocardiography

Although improved accuracy of contrast-enhanced images is not restricted to patients with a poor baseline image quality, it is especially important in this group. Even with new ultrasound equipment, the percentage of suboptimal images can range from 10% to 15%. The problem is even greater for stress echocardiography because as many as 33% of images
are suboptimal owing cardiac movement and hyperventilation during stress.

It has been estimated that the addition of contrast media provides 37% more diagnostic information and, in patients with a poor acoustic window, a 50–90% improvement has been observed.

The utility of contrast enhancement of endocardial border definition in echocardiography has been shown in various studies. Detailed assessments of global and regional wall motion abnormalities and evaluation of various pathologies of the LV, such as LV thrombotic masses, LV non-compaction and apical hypertrophy, are possible with contrast imaging.

Several studies have also demonstrated that contrast-enhanced echocardiography improves the evaluation of LV volumes and EF, which provides valuable diagnostic and prognostic information in patients with suspected CAD.

Image quality is a critical factor in accuracy of stress echocardiography, and previous studies have shown that good endocardial definition is required for accurate WMA. Contrast has been shown to improve visualization of regional wall motion abnormalities, improve study quality and increase reader confidence in study interpretation. The high success rate of contrast enhancement in the evaluation of the wall motion has been shown in rest and stress echocardiography. Myocardial opacification also occurs with contrast imaging, providing important information about coronary perfusion and enabling detection of subtle wall motion abnormalities by combining impaired perfusion and wall motion. Therefore, it appears to be reasonable to use contrast routinely in stress echocardiography.

Myocardial contrast echocardiography

The development of new ultrasound contrast agents and imaging techniques has now made possible the assessment of myocardial perfusion with echocardiography. Active gas-filled microspheres (microbubbles), which have similar properties to red blood cells, are utilized for assessing coronary microcirculation. After injection of a myocardial contrast agent, destruction of microbubbles in the myocardium and replenishment of contrast within the myocardium can be observed within a few seconds. A decrease in myocardial blood flow (MBF) due to impaired coronary flow prolongs replenishment time in proportion to the reduction in MBF.

Myocardial contrast echocardiography can be used in assessing chronic coronary artery disease, acute coronary syndromes (ACS) and hibernating myocardium.

Chronic CAD

Although exercise stress is the most frequent stressor in the assessment of wall motion abnormality, vasodilator stress is better than exercise or dobutamine in MCE because it facilitates acquisition of more comprehensive images. Five cardiac cycles are required for the appearance of contrast in normally perfused myocardium. This is reduced to two cycles with stress because of increasing myocardial flow. A delayed contrast appearance and reduced contrast intensity forms the basis for detection of CAD. Many studies have demonstrated concordance between MCE and SPECT during rest or stress, and these suggest that MCE is a reliable technique for the diagnosis of coronary artery disease. The sensitivity and specificity for the detection of CAD is 83% and 80%, respectively, according to the analysis of European Association of Echocardiography.

Acute coronary syndromes

Myocardial contrast echocardiography allows immediate simultaneous assessment of wall motion and perfusion and offers an important role in the diagnosis of ACS. The portability of MCE to the bedside makes it a very powerful tool in assessment of patients with ACS. It was found, in a large multicentre study, that MCE improved the detection of ACS with clinical electrocardiography (ECG) and biochemical markers in patients with chest pain, and it was found equivalent to SPECT for risk stratification. In one study, the incremental prognostic benefit of MCE over conventional parameters and regional function by echocardiography were shown in over 1000 patients. In another study, assessment of resting perfusion and function with MCE was shown to be superior to the thrombolysis in myocardial infarction (TIMI) risk score for diagnosis and prognostication in patients presenting to the emergency department with chest pain and a non-diagnostic electrocardiogram. Studies have also reported high sensitivities with MCE to detect ACS compared with standard echocardiography and SPECT. Hence, MCE is a clinically useful imaging tool in the management of patients with undiagnosed chest pain in the emergency department.
Myocardial viability

Myocardial contrast echocardiography can identify viable myocardium, and identification of viable myocardium is important because it is useful in predicting recovery of LV function after revascularization in patients with AMI and chronic ischaemic LV dysfunction. The ability of MCE to predict functional recovery is similar to that of cardiac magnetic resonance (CMR) imaging. MCE may be particularly useful in further evaluation of myocardial viability in dobutamine-non-responsive myocardium because MCE has superior sensitivity and equivalent specificity to dobutamine echocardiography and it has also equivalent sensitivity and superior specificity to SPECT imaging for the detection of myocardial perfusion PET, can be calculated.

Summary of perfusion agents

For further details, the reader is referred to Clinical Nuclear Cardiology: State of the Art and Future Directions by Zaret BL.

Thallium-201

Thallium-201 is a K⁺ analogue and its uptake depends on blood flow and extraction fraction (approximately 85%). Uptake requires Na⁺/K⁺-ATPase of the cellular membrane and hence requires viable myocardium. It is not bound intracellularly and can diffuse back to circulation (also called redistribution). Disadvantages include the relatively long half-life of 73 hours, which results in increased radiation exposure to the patient. In addition, its physical properties are not ideal for imaging because of the low-energy (69–80 keV) photons that are attenuated in soft tissues and cause greater scatter. Redistribution half-life is approximately 4–8 hours. Although ²⁰¹Tl has been the standard for nuclear MPI for many years, it has largely been replaced by the technetium-⁹⁹ᵐ (⁹⁹ᵐTc)-labelled radiopharmaceuticals owing to ²⁰¹Tl’s high radiation exposure to the patient, significant attenuation from soft tissues and need for daily production and transfer to departments.

Technetium-⁹⁹ᵐ-labelled tracers

⁹⁹ᵐTc has a half-life of 6 hours and 140-keV photons that are ideal for gamma camera imaging. ⁹⁹ᵐTc-sestamibi (Cardiolite®; Lantheus Medical Imaging, North Billerica, MA, USA) and ⁹⁹ᵐTc-tetrofosmin (Myoview®; GE Healthcare, Princeton, NJ, USA) are lipophilic monovalent cationic agents currently used. First-pass extraction fraction of sestamibi is 65% and of tetrofosmin is 54%. The lower extraction fraction than ²⁰¹Tl translates into lower perfusion differences between the segments supplied by normal and stenosed coronary arteries, making the distinction of stenotic segments more difficult. These agents are passively taken into the cell with the help of their lipophilicity and electrical activity.
gradient across viable cell and mitochondrial membranes. Their liver uptake may interfere with cardiac uptake and requires a certain waiting period between injection and imaging.

$^{99m}$Tc-teboroxime (Cardiotec®; Squibb Diagnostics, Princeton, NJ, USA) is a neutral lipophilic compound with high (90%) first-pass extraction fraction. It has a rapid washout from the myocardium; thus, it requires fast imaging before the contrast between normal and stenotic segments is lost. Teboroxime is currently not marketed. Another $^{99m}$Tc-labelled compound is $^{99m}$Tc-NOET. NOET, like $^{201}$Tl, has a high extraction fraction and exhibits redistribution. It is reported to have higher cardiac and pulmonary uptake than sestamibi and tetrofosmin.\textsuperscript{92} Both teboroxime and NOET are not located intracellularly and are called pure perfusion tracers.

**Positron-emitting isotopes**

$^{82}$Rubidium ($^{82}$Rb) is a K+ analogue that has a half-life of 75 seconds. It is eluted from a strontium–rubidium generator and its short half-life allows serial rest and stress studies. Its first-pass extraction fraction is approximately 60%. $^{13}$N-ammonia has a half-life of 10 minutes and is freely diffusible across membranes. It is either used in the synthesis of glutamine or diffuses back to the circulation. $^{13}$N-ammonia has an extraction fraction of up to 90%.

**Role of nuclear medicine in ischaemic heart disease**

The ischaemic cascade (Figure 6) gives an advantage to nuclear MPI to detect abnormalities earlier than wall motion abnormalities or ECG changes detected by other modalities.\textsuperscript{93} Detecting the signal early in the cascade may result in relatively lower specificity and lower PPV for significant stenosis.

As with most diagnostic tests, nuclear MPI works best with an intermediate pre-test probability.\textsuperscript{94,95} Although what exactly defines an intermediate probability is not strictly established, 20–80% or 10–90% has been proposed.\textsuperscript{96} Pre-test assessment of probability is important in order to avoid excessive false-positive or false-negative results.

Inappropriate use of procedures may have a negative economical impact. In patients with a pre-test probability of less than 80%, invasive coronary angiography as first test was
shown to not be cost-effective.97,98 Performing nuclear MPI before cardiac catheterization has shown to provide cost savings rather than directly proceeding to coronary angiography.99,100 It should also be noted that as reimbursements for non-invasive procedures are decreasing, cost-effectiveness comparisons may be more favourable for these procedures.

Sensitivity and specificity

The diagnostic performance of nuclear MPI has been researched in many studies101,102. It has been shown to have sensitivity of between 87% and 91% and specificity between 70% and 81%, while pharmacological and exercise stress has similar diagnostic accuracies.101,102

While expert analysis of MPI may be matched by use of quantitative analysis of images, quantitation is known to be more reproducible103 and may additionally decrease intra- and inter-observer variability.

Electrocardiography-gated image acquisition (i.e. gated SPECT) has been reported to increase observer accuracy avoiding false-positive interpretations due to attenuation artefacts by identifying normal motion at apparently fixed perfusion defects.104,105 False-positive findings due to attenuation have been decreased by use of technetium-labelled tracers instead of thallium,106 but the evaluation of images from women and obese patients is still problematic. Especially in these groups, the use of methods such as attenuation correction by CT/transmission images or alternating patient position is known to increase diagnostic accuracy.105,107–110

It is also debated whether the anatomical/luminal evaluation of coronary angiography should be the reference standard against which to compare nuclear MPI, because of the known interobserver variability, limitation in evaluating eccentric lesions and diffusely affected vessels.87,111 Coronary flow reserve may be a better measure to compare with stress-rest MPI.112 However, in the case of multivessel disease, discordance between fractional flow reserve (FFR) and MPI findings has been reported.113 Absolute coronary flow and flow reserve calculation with PET may be a better measure to compare with invasive FFR findings.114

American Heart Association (AHA) 2012 guidelines115 give a class I indication of nuclear MPI for suspected stable ischaemic heart disease for patients with intermediate to high pre-test probability and uninterpretable baseline ECG (with pharmacological stress if unable to exercise) and a class IIa to patients with the same range of pre-test clinical probability and interpretable baseline ECG. In the case of low pre-test probability, AHA 2012 guidelines do not recommend nuclear MPI.

Prognostic information

As nuclear MPI can detect functionally significant CAD, it can provide important information on prognosis. The prognostic value of nuclear MPI has been established in various studies.116–120 Several prognostic variables and several high-risk factors have been identified: summed stress score, LVEF, post-stress left ventricle dilatation,121,122 increased pulmonary uptake of radiotracer,123 increased right ventricular uptake, change in localization of maximal tracer uptake (masking ischaemia as reported in multivessel disease),124 along with ischaemic ECG changes.125

A normal exercise nuclear MPI predicts less than 1% annual risk of AMI or cardiac death in both men and women, although an increase in the severity of the abnormalities increases event rate, as does the presence of high-risk factors such as low EF or transient ischaemic dilatation.116,125 A normal pharmacological stress nuclear MPI study predicts a higher risk of cardiac events than a normal exercise nuclear MPI.126 With the use of variables, predicted event risk can be calculated.127

For patients with known stable ischemic heart disease (SIHD) and risk assessment, AHA 2012 guidelines assign a class I recommendation of nuclear MPI for patients with uninterpretable baseline ECG and class IIa if baseline ECG is interpretable. Regardless of baseline ECG, if a patient is unable to exercise, a class I recommendation is given for nuclear MPI with pharmacological stress for risk assessment. If considered for revascularization of known stenosis of unknown physiological significance, nuclear MPI again has a class I recommendation.115

Revised cardiac risk index is used to evaluate patients for perioperative cardiac complications of non-cardiac surgery.128 Revised cardiac risk index combines five
factors, one of which is history of ischaemic heart disease, and nuclear MPI has been included in several guidelines to assess perioperative cardiac risk.\textsuperscript{129,130} Non-invasive testing, including nuclear MPI, is recommended in patients who will have intermediate-risk surgery, a revised cardiac risk index score of $\geq 1$ and poor functional capacity [<4 METs (metabolic equivalents)].\textsuperscript{131}

**Acute chest pain**

Nuclear MPI with injection of either sestamibi or tetrofosmin during chest pain in the emergency department identifies the presence of ischaemic coronary disease. Since there is no redistribution of either radionuclides imaging of the patient may be performed several hours after injection, when the patient’s clinical condition has stabilized. Nuclear MPI identifies patients requiring invasive intervention and provides prognostic information.\textsuperscript{132} Integration of nuclear MPI into management of suspected ACS leads to a lower rate of unnecessary catheterization, less unnecessary hospitalization and lower overall costs.\textsuperscript{133} Patients who will benefit from nuclear MPI are defined as having no prior myocardial infarction (MI), having a non-diagnostic or a normal ECG and having suspicion of acute ischaemia.\textsuperscript{134}

**Special populations**

**Diabetes** The risk of MI in a patient with diabetes is similar to that of patients without diabetes but with previous MI.\textsuperscript{135} There are contradictory results of studies on whether percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) has a beneficial effect on survival in diabetic patients.\textsuperscript{115,136,137} Studies have shown that survival in diabetic patients designated high risk based on the results of nuclear MPI is better following CABG than medical therapy.\textsuperscript{138} Normal MPI in a diabetic patient is associated with a higher risk than in patients without diabetes; and increasing ischaemic extent defined in nuclear MPI further risk stratifies patients with diabetes.\textsuperscript{139}

**Chronic kidney disease** Chronic kidney disease is a risk factor for ischaemic heart disease and is associated with worse outcomes after interventions.\textsuperscript{115,140} There are studies reporting that CABG may be more beneficial than medical therapy.\textsuperscript{141} Nuclear MPI is shown to risk stratify patients with all stages of chronic kidney disease.\textsuperscript{142}

**Women** Detection of ischaemic heart disease is more problematic in women because exercise stress ECG changes are less specific and women have lower exercise capacity as well as other comorbidities. Imaging studies after standard exercise ECG stress test offer improved accuracy in diagnosis and risk stratification in women.\textsuperscript{143}

**Future**

Probes for plaque inflammation (for example, \textsuperscript{18}F-fluorodeoxyglucose) and calcification (Na-\textsuperscript{18}F), imaged by PET, are being actively investigated for evaluation of plaque composition and progression.\textsuperscript{144}

Measurement of absolute MBF with PET is possible with \textsuperscript{82}Rb, \textsuperscript{13}N-ammonia (Figure 7), oxygen-15 (\textsuperscript{15}O)-labelled water and possibly with \textsuperscript{18}F-Flurpiridaz (in phase III trial). Measurement of MBF under the influence of vasodilators should be the counterpart of FFR measurements of angiography offered in the nuclear medicine department.\textsuperscript{146}

A recently developed PET perfusion agent labelled with \textsuperscript{18}F, Flurpiridaz, offers quantification of MBF and detection of ischaemic heart disease. It has been

**FIGURE 7** Short-axis MBF images obtained with \textsuperscript{13}N-ammonia in a healthy volunteer. Acquired at rest, after adenosine (ADO), and dobutamine (DBTMN). The colour scale shown on the right represents ml/min/g. Reprinted from *JACC Cardiovasc Imaging*, vol. 4, Gewirtz M, Cardiac PET: a versatile, quantitative measurement tool for heart failure management, pp. 292–302, 2011, with permission from Elsevier.\textsuperscript{145}
shown to be safe and offers improved accuracy compared with SPECT.\textsuperscript{147,148}

As a result of development of faster gamma cameras and software algorithms by major vendors, similar image quality can now be achieved in a fraction of time, thus offering the opportunity to decrease radiotracer dose and radiation exposure to the patient.\textsuperscript{149} Studies have shown similar diagnostic accuracies with these new systems, which offer more patient comfort and lower radiation exposure.\textsuperscript{150}

\textsuperscript{123}I-labelled beta-methyl-iodophenylpentadecanoic acid (\textsuperscript{123}I-BMIPP) is a radioiodinated branched-chain fatty acid that has been shown to detect persistent metabolic changes after recovery from an episode of ischaemia called ‘ischaemic memory’.\textsuperscript{151} Ischaemia may cause the myocardium to shift its metabolism from fatty acids to glucose, and this shift can persist after recovery of ischaemia. Since BMIPP reflects previous ischaemia, it holds great potential for patients with acute chest pain as it can show abnormalities many hours after an ischaemic episode.\textsuperscript{115,152}

\textsuperscript{123}I-labelled meta-iodobenzylguanidine (\textsuperscript{123}I-MIBG) is known to reflect cardiac sympathetic innervation and is reported to predict risk of fatal arrhythmias in heart failure patients and may help determine which patients will benefit from implantable cardioverter–defibrillator treatment.\textsuperscript{151,153}

**Cardiac magnetic resonance imaging**

Cardiac magnetic resonance imaging (nuclear magnetic resonance (MR) of the heart) has a very important role in diagnosis and management strategies of coronary heart disease (CHD) and has diverse applications ranging from volumetric measurements to viability assessment. Although no other cardiac imaging modality is capable of giving as much information as CMR, it is not as widely or commonly used as it should be, or is expected to be. The main reasons for rare usage of CMR are twofold. First, CMR is time-consuming, with one study lasting 45–70 minutes. Also, it is a relatively new and expensive technique compared with the other cardiac imaging modalities. Choosing the most cost-effective technique results in less frequent use of CMR. Secondly, practitioners do not commonly know the indications and the strength of CMR. Despite these limitations, CMR is certainly one of the most promising imaging modalities used in the evaluation CHD.

In patients with a possible or settled diagnosis of CHD, the information required includes wall motion abnormalities, LVEF, volumes of the heart chambers, myocardial contractility response to dobutamine, structural changes and viability of the heart and the complications of ischaemia. At present, CMR is probably the only imaging modality that can provide information in all these areas.

The most important role of CMR in the evaluation process of CHD is establishing the need for catheterization in diagnostic approach and the need for further invasive treatment in prognostic approach. Reducing the number of unnecessary and invasive diagnostic procedures makes the seemingly high-cost CMR cost-effective.

**Functional imaging in coronary heart disease**

By using balanced steady-state free precession (SSFP) technique (implemented as FIESTA(GE Medical System; Buckinghamshire, UK)/true-FISP(Siemens; Munich, Germany)/b-FFE(Philips; Amsterdam, Netherlands) depending on manufacturer) dynamic images with a high resolution can be obtained to study ventricular function (i.e. cine MRI). Owing to the high resolution, high sampling rate and clear pictures, cine MRI is accepted as the gold standard for the assessment of regional and global LV function. Cardiac magnetic resonance imaging provides superior detection and quantification of the LV wall motion abnormalities compared with 2D TTE, 3D TTE, 64-row contrast CT and 3D echocardiography.\textsuperscript{154} The SSFP technique significantly improves endocardial border delineation without contrast agents. By improving endocardial border definition, SSFP assesses cardiac volumes and EF accurately.\textsuperscript{155} Evaluation of ischaemia-induced wall motion abnormalities can be performed by dobutamine stress MRI (DSMR). Nagel \textit{et al.}\textsuperscript{156} reported that DSMR has higher diagnostic accuracy than DSE in the detection of wall motion abnormalities. Dobutamine stress MRI can also be used for follow-up of patients after coronary revascularization procedures.\textsuperscript{157} Cine MRI may also be used for the evaluation of the complications of CHD such as LV thrombosis and aneurysm formation. 3-T CMR may potentially be used for functional imaging but it has more artefacts than 1.5-T CMR. In routine clinical practice, 1.5-T CMR is used for functional imaging.
**Magnetic resonance coronary artery imaging**

Although magnetic resonance coronary angiography (MRCA) is a non-invasive and radiation-free modality for imaging the coronary arteries, its diagnostic accuracy for CAD is still not high and further technical development is needed for visualization of cardiac and respiratory motion and small coronary vessels. Even a recent study reported that CMRA is useful modality for predicting the future cardiac event risk in patients with suspected CAD but the current application of coronary artery imaging by CMRA is restricted to research purposes. A definite indication for MRCA is non-invasive visualization of coronary artery anomalies.

**Assessment of myocardial viability in coronary heart disease**

Viability assessment (distinguishing the viable myocardium from the necrotic tissue) in patients with CHD plays a pivotal role in further coronary revascularization procedures and in prognosis. Different imaging modalities such as PET, SPECT and DSE can evaluate the viability with high diagnostic accuracy rates. Among them, SPECT is most widely used and most extensively validated whereas PET has the highest diagnostic accuracy. Contrast-enhanced MRI provides structural information on the myocardium and its excellent spatial resolution and tissue characterization enables it to detect viable myocardium accurately. Klein et al. and Kühl et al. reported the diagnostic accuracy of contrast-enhanced CMR (delayed enhancement CMR) in the assessment of myocardial viability with a high accuracy, compared with FDG-PET, in patients with coronary artery disease and LV systolic dysfunction. Wagner et al. compared delayed-enhancement MRI with SPECT and found that subendocardial infarcts were detected by delayed enhancement CMR imaging in 92%, whereas SPECT detected only 28%. Hillenbrand et al. found that when the transmural extent of hyperenhancement was < 25%, improvement of systolic function is very likely (87%), whereas, when the extent of hyperenhancement was > 75%, functional recovery was unlikely. A similar research study supported this finding (Figure 8). Combination of delayed-enhancement CMR imaging and evaluation of segmental wall motions by SSFP yields better prediction of contractile reserve. In cases with intermediate degrees of hyperenhancement (> 25% to < 75%), the thickness and the thickening of the related myocardial segment may help to understand if dysfunctional segments are viable and have the ability to recover function. Thin segments with severe hypokinesia are less likely to recover after revascularization. Assessment of inotropic reserve with dobutamine is also important in cases with intermediate degrees of hyperenhancement to define the viable myocardium. Among imaging modalities, the unique feature of CMR is its ability to assess different markers of viability in a single study. As mentioned above, CMR has the capability to assess wall thickness, contractile reserve, hyperenhancement and perfusion together (see below), all of which are important markers in viability assessment. Currently, there is no other imaging technique that offers similar advantages. Considering the greater spatial resolution compared with PET, CMR imaging has the potential to replace or complement other commonly used techniques in the viability assessment of the myocardium. Cardiac magnetic resonance imaging has the unique ability of reliable and accurate assessment of myocardial viability and scar burden, coronary perfusion, and contractile reserve with optimal image quality and low inter- and intraobserver agreement.

**Assessment of myocardial perfusion in coronary heart disease**

Cardiac magnetic resonance perfusion imaging is a non-invasive method for determining MBF and perfusion findings can be combined with the assessment of wall motion abnormality. The most frequently used approach to assess myocardial perfusion with CMR is monitoring the first pass of a contrast medium through the heart. The contrast medium given to systemic veins firstly passes through pulmonary vessels, then to the left heart chambers, coronary arteries and lastly to the myocardium. The measurements can be carried out during baseline conditions and during maximal hyperaemia induced with either adenosine or dipyridamole. The same contrast medium can be used for delayed-enhancement study afterwards.

Analysis of the MR perfusion images can be qualitative, semiquantitative or quantitative. Visual analysis is often used clinically and is a fast, but less accurate, approach.

Studies have compared CMR perfusion with $^{201}$TI and $^{99m}$Tc radionuclide imaging and coronary angiography to detect CAD. All studies showed no inferiority...
of CMR perfusion. Hartnell et al.\textsuperscript{170} reported an improved accuracy for MR myocardial perfusion when combined with associated wall motion abnormalities.

Assessment of myocardial metabolism in coronary heart disease

Although technical challenges presently limit the clinical utility of MR spectroscopy (MRS), this technique is used in experimental cardiology for the study of cardiac metabolism.\textsuperscript{171,172} The phosphocreatine/ATP ratio decreases in cases of ischaemia, which is one of the first changes in the myocardium in response to ischaemia. Magnetic resonance spectroscopy is beyond the scope of this paper.

Conclusion

Further progress will depend on successful dissemination of the techniques for perfusion quantification among the CMR community.

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