Non-invasive anatomical and functional imaging for the detection of coronary artery disease

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Coronary artery disease (CAD) is still an important cause of morbidity and mortality in the Western world. The gold standard for assessing significant coronary artery stenosis is invasive coronary angiography. Several disadvantages of the technique in combination with the fact that a substantial number of patients referred for conventional angiography appear free from significant stenosis have led to the pursuit of non-invasive imaging modalities for the diagnosis of CAD. The traditional modalities for this purpose are gated single-photon emission computed tomography, position emission tomography, (contrast) stress echocardiography and cardiac magnetic resonance (CMR), and these techniques can be characterized as functional imaging techniques as they detect ischaemia. Although the presence of a flow-limiting stenosis can be adequately ruled out with these techniques, atherosclerosis cannot be visualized with functional techniques. For this purpose, non-invasive coronary angiography techniques (computed tomography and CMR) are currently under development. The purpose of this review is to provide the reader an overview of the currently used imaging modalities to detect CAD.

Introduction

Coronary artery disease (CAD) is currently the leading cause of death in the Western world today with still increasing prevalence. The gold standard for the detection of CAD is conventional coronary angiography, which has excellent resolution and allows direct visualization of the coronary lumen. However, conventional angiography has several drawbacks that need to be considered. First, it is an invasive technique with potential (small) risk for serious complications. Furthermore, the costs of this procedure are significant. Bearing in mind that a number of procedures will be performed in patients in whom no evidence for clinically important CAD will be demonstrated, attention has shifted to
the development of non-invasive techniques to accurately detect or rule out the presence of CAD. Modalities that are traditionally used for this purpose are single-photon emission computed tomography (SPECT), positron emission tomography (PET), (contrast) stress echocardiography and cardiac magnetic resonance (CMR) imaging. With these techniques, the haemodynamic consequences of coronary artery stenoses can be assessed by detecting the presence of perfusion abnormalities or left ventricular (LV) systolic dysfunction. However, although with these techniques the presence of a significant flow-limiting coronary stenosis can be adequately ruled out, the presence of non-flow-limiting coronary atherosclerosis cannot be demonstrated. Nonetheless, as increasing interest is directed towards early detection in particular, the knowledge of preclinical CAD may be of great value for patient management and may substantially improve outcome. Therefore, extensive research is currently carried out in the field of non-invasive anatomical imaging, for instance, in the evaluation of coronary calcium burden or non-invasive coronary angiography with multislice computed tomography (MSCT) and CMR.

The purpose of this review is to provide the reader an extensive overview of the currently used imaging modalities to detect CAD.

**Anatomy and atherosclerosis**

**Multislice computed tomography**

**Calcium score**

Computed tomography (CT) has been available for cardiac imaging since the early 90s. The first investigations were performed with electron beam CT (EBCT), predominantly for the assessment of coronary calcium scores. With EBCT, X-rays are created through an electron beam that is guided by a 210° tungsten ring in the gantry and images are acquired in a step and shoot mode. In contrast, MSCT scanners are equipped with multiple detector rows that allow simultaneous acquisition of a number of slices with a certain overlap. Although MSCT can also be used for calcium score, most data thus far have been acquired with EBCT because this scanner is associated with lower radiation dose and superior reproducibility when compared with MSCT. Quantification of calcium in the coronary arteries can be realized with the Agatston score.\(^1\) In general, a score of 1–10 is considered minimal, 11–100 mild, 101–400 moderate and >400 severe calcification. Assessment of coronary calcium score is particularly valuable for the prognosis of asymptomatic patients with a low to intermediate likelihood of CAD (e.g. range 15–50%), based on sex, age and risk factors. Raggi et al.\(^2\) demonstrated in 267 subjects without coronary artery
calcium a low short-term risk of death (1.2%), even in the presence of diabetes mellitus. A group of 10377 asymptomatic individuals who underwent EBCT for coronary calcium screening was followed by Shaw et al.\(^3\) A 5-year risk-adjusted survival for patients with a calcium score of \(\leq 10\) of 99.0% was observed, whereas a significantly worsened (95%, \(P < 0.001\)) risk-adjusted survival was noted for patients with extensive calcium scores of \(>1000\). The authors noted that coronary calcium score provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality. Figure 1 provides an example of a patient with a high calcium score.

**Coronary angiography**

With the introduction of the MSCT, the first step towards non-invasive evaluation of the coronary arteries with CT techniques was taken. Although the initial results with the four-slice MSCT were promising, 20% of the coronary segments had to be excluded from evaluation due to

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**Fig. 1** Example of a patient with a high calcium score. Ao, aorta; D, diagonal branch of the left anterior descending coronary artery; LM, left main coronary artery; LAD, left anterior descending coronary artery. Calcifications appear as bright white dense structures on the MSCT images.
to non-diagnostic quality.\textsuperscript{4} The introduction of the 16-slice and at present the 64-slice MSCT has led to substantial improvement in resolution due to submillimetre collimation and faster rotation times. Recently, the accuracy of the 64-slice MSCT has been investigated in a non-selected patient population ($n = 69$ patients).\textsuperscript{3} Invasive coronary angiography was used as the gold standard for the assessment of significant coronary artery stenosis (defined as $\geq 50\%$ decrease in luminal diameter). All coronary segments were included in the analysis, regardless of the diameter of the vessel. An overall sensitivity of 90\% was demonstrated for the detection of significant coronary stenosis, whereas the overall specificity was even higher, 94\%. Similar percentages were observed in the analysis of stented lesions. Eight per cent of all segments were of non-diagnostic quality. A meta-analysis based on 1778 patients\textsuperscript{4,6–13} (Fig. 2) shows that the weighted mean sensitivity and mean specificity for the detection of significant CAD have increased to 91 and 96\%, respectively, with the 64-slice MSCT scanner.

Nevertheless, certain shortcomings of the technique need to be mentioned. Non-invasive evaluation of the coronary arteries with MSCT can be hampered by severely calcified plaques and stents as they can cause partial volume artefacts, which, in turn, obscure the coronary lumen. Another important limitation of non-invasive angiography with MSCT is the radiation burden and techniques to reduce radiation dose are currently investigated.

**Plaque imaging**

An important advantage of non-invasive coronary angiography with MSCT when compared with conventional coronary angiography is the ability to image the atherosclerotic lesions directly and it may allow

\begin{figure}[h]
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\includegraphics[width=\textwidth]{Fig_2}
\caption{Diagnostic accuracy of four slice, 16-slice and 64-slice MSCT for the detection of significant CAD.}
\end{figure}
distinction between different plaque types. Indeed, Schroeder et al.\textsuperscript{14} significantly demonstrated different mean densities of $419 \pm 194$, $91 \pm 21$ and $14 \pm 26$ HU for, respectively, calcified, mixed and soft plaques (as classified by intravascular ultrasound (IVUS)). Ideally, this information would potentially allow identification of patients at elevated risk of coronary events based on the plaque distribution and type. Unfortunately, data are currently scarce, and also further distinction of low-density plaques in fibrous and lipid content appears at least not feasible in the near future as their signal intensities on MSCT are highly overlapping.

**Cardiac function**

Although MSCT imaging is primarily performed for the non-invasive evaluation of the coronary arteries, information on cardiac function can be derived simultaneously without the need for additional acquisitions. Using the ECG tracing with retrospective ECG gating, it is possible to reconstruct images and to create cine loops at every desired phase of the cardiac cycle. By determining the end-diastolic and end-systolic phase, LV volumes and ejection fraction (EF) can be evaluated, as well as regional wall motion. Belge et al.\textsuperscript{15} demonstrated strong correlations between 16-slice MSCT and cine CMR for the assessment of LVEDV ($r = 0.92$, $P < 0.001$), LVESV ($r = 0.95$, $P < 0.001$) and LVEF ($r = 0.95$, $P < 0.001$). Even higher correlations were found by Raman et al.\textsuperscript{16} with correlation coefficient of $r = 0.97$ for all above-mentioned parameters. However, owing to the relatively high radiation dose, MSCT imaging for the evaluation of cardiac function alone is currently not preferable. The duration of an MSCT angiography examination ranges from 10–15 min, depending on the imaging protocol used. The actual scan time has been reduced to $\sim 10$ s with the introduction of the 64-slice MSCT. Accordingly, the majority of procedural time is used for patient preparation and determining of scanning positions.

**CMR imaging**

CMR is a relatively new imaging modality in the cardiac arena. In a short time span, the technique has been established as a useful tool for non-invasive cardiac imaging as it combines excellent spatial and temporal resolutions with the absence of radiation burden.

**Coronary angiography**

In recent years, the development of ultra fast imaging sequences has enabled coronary imaging with CMR. In 2001, Kim et al.\textsuperscript{17} have investigated the accuracy of coronary angiography with CMR in 109 patients with suspected CAD in a prospective, multicentre study.
In each patient, seven coronary segments were evaluated, and 84% of all coronary segments were interpretable with CMR. An overall accuracy of 72% for diagnosing CAD with CMR was found. Combination of both free-breathing coronary CMR angiography and breathhold CMR angiography has been demonstrated to further improve the detection of significant coronary artery stenoses when compared with free-breathing alone. A meta-analysis of 28 studies (n = 903 patients), directly comparing non-invasive coronary angiography with CMR and conventional angiography, showed a weighted mean sensitivity of 72% and a specificity of 87%. Nevertheless, diagnostic accuracy and the percentage interpretable segments are still not sufficient for routine clinical application, although acquisition times are also still relatively long with CMR. Major challenges for clinical applicability are the spatial resolution and coverage, compensation for cardiac and respiratory motion and signal-to-noise limitations. The duration of a CMR investigation strongly depends on the imaging protocol used. For most protocols, the time needed will range from 30–60 min, including patient preparation. The technique is less suitable for patients with severe claustrophobia and for patients with cardiac pacemakers.

**Plaque imaging**

Experimental studies have suggested a role for CMR to track the progression of atherosclerosis. Evaluation of coronary plaque is currently limited because of the small size and motion of the coronary arteries. However, promising results have been obtained in larger vessels, including the carotids and the thoracic aorta. Toussaint et al. were able to characterize different components of carotid lesions. In addition, serial imaging with CMR allows following the progression or regression of atherosclerotic lesions over time, thereby enabling monitoring the therapeutic effect of anti-atherosclerotic strategies. Saam et al. recently evaluated the ability of CMR to quantify major carotid atherosclerotic plaque components in vivo. The authors included 31 patients scheduled for carotid endarterectomy and showed an excellent agreement between CMR measurements of plaque components and pathological findings after endarterectomy. Although CMR plaque imaging is currently still limited to larger vessels, much is expected by the development in external coils as well as contrast agents that may enhance different vessel wall components.

**Detection of ischaemia**

Traditionally, non-invasive imaging techniques have aimed for the detection of the functional consequences of significant CAD by visualization...
of perfusion defects or regional wall motion abnormalities. According to a process known as the ischaemic cascade, perfusion abnormalities are induced at an early stage, followed by diastolic and systolic LV dysfunction (Fig. 3). Suitable imaging modalities for this purpose are gated SPECT, PET, stress echocardiography (with contrast) and CMR.

**Nuclear imaging**

**Single-photon emission computed tomography**
Evaluation of myocardial perfusion with stress and rest myocardial perfusion SPECT has become a cornerstone in the management of patients with known or suspected CAD. In patients with CAD, the decrease in myocardial blood flow through a stenosed vessel will precede the occurrence of wall motion abnormalities. As a result, perfusion SPECT allows earlier detection of CAD when compared with imaging modalities that rely on the induction of wall motion abnormalities.

**Myocardial perfusion**
For the evaluation of myocardial perfusion, two data sets are commonly acquired: one at rest and one after (physical or pharmacological) stress. The presence of reversible (indicating ischaemia) and irreversible (indicating scar tissue) perfusion defects is considered to be indicative of CAD. An example of a patient with a reversible defect as well as an irreversible defect on perfusion SPECT is provided in Figure 4. Three

![Fig. 3 The ischaemic cascade reflecting the order in which pathophysiological changes during ischaemia will occur.](image-url)
tracers are available for the assessment of myocardial perfusion: thallium-201, technetium-99 m sestamibi and technetium-99 m tetrofosmin. The technetium-99 m labelled tracers are most frequently used owing to their higher photon energy and shorter half-life. Perfusion SPECT is very sensitive for the detection of CAD, because perfusion abnormalities occur early in the ischaemic cascade. However, specificity is lower, which is mainly due to referral bias: a patient with a normal test will only be referred for conventional angiography when the patient is at high risk for CAD. To correct for referral bias, the term ‘normalcy’ has been introduced, which is the percentage of normal perfusion SPECT studies in a population with low likelihood for CAD.25 Pooling of 10 SPECT studies, as performed by Underwood et al.,25 showed, indeed, a weighted normalcy of 89%.

In addition to detection of CAD, the technique can also be used for prognostification. Indeed, a normal SPECT study has been demonstrated to indicate excellent prognosis with an annual risk of cardiac death of <1%.26 In contrast, patients with an abnormal SPECT study have been shown to have an annual event rate of 6.7%.25

Cardiac function
With the introduction of electrocardiographic gating, simultaneous measurement of LV volumes and EF as well as evaluation of regional

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**Fig. 4** Example of a patient with a reversible defect as well as an irreversible defect on perfusion SPECT. Example of a patient with reversible perfusion defect in the inferior (white arrows short-axis images) and anterior wall (white arrows vertical long-axis images), and an irreversible perfusion defect in the septum (arrow heads short-axis and horizontal long-axis images). The upper panel shows from left to right the short axis, the vertical long axis and the horizontal long axis reconstructions after stress and the lower panel shows the same reconstructions during rest.
wall motion has become routine practice. A meta-analysis of nine studies \((n = 164\) patients) revealed excellent correlations between gated SPECT and CMR for the evaluation of LV volumes and EF.\(^{27}\) In addition, an excellent agreement of 83% between gated SPECT and CMR for the assessment of regional LV function has been demonstrated.\(^{28}\) As LVEF is an important prognostic parameter, the addition of functional information has, not surprisingly, been shown to add to the prognostic value of a SPECT study.\(^{29}\) Also, the functional data can be used to differentiate between true fixed defects and attenuation artefacts. Accordingly, the number of ‘borderline normal’ and ‘borderline abnormal’ interpretations may be significantly reduced by gating of the scan, as has been demonstrated by Smanio et al.\(^{30}\)

The duration of a gated perfusion SPECT is \(\sim 15\) min, depending on the imaging protocol used. The complete investigation including stress will take \(\sim 60\) min of patient contact time, although delays between images add to the total time. The main limitation for the patient is the radiation burden.

**Positron emission tomography**

*Myocardial perfusion*

Imaging of myocardial perfusion with cardiac PET has several important benefits over gated SPECT imaging. In contrast to SPECT, which measures relative perfusion, PET has the ability to quantify myocardial perfusion in absolute terms (millilitres per gram per minute), which may be important in patients with homogeneous reduced perfusion (e.g. patients with heart transplants or with balanced ischaemia in whom regional differences in perfusion are not obvious). In addition, the physical characteristics of the PET tracers allow systematic accurate attenuation correction. For the evaluation of myocardial perfusion with PET, three different tracers can be used: two tracers that are extracted (rubidium-82 and nitrogen-13 ammonia) and one tracer that is freely diffusible (oxygen-15 water). Rubidium-82 (Rb-82) has a short half-life of 76 s and is partially extracted by the myocardium during a single capillary transit. The short half-life allows rapid completion of a series of resting and stress myocardial perfusion examinations and, therefore, Rb-82 is a very suitable and efficient radioisotope for routine clinical practice. Another advantage of Rb-82 is that it can be produced by a commercially available generator, thus obviating the need for a cyclotron. However, the most commonly used radioisotope for myocardial perfusion imaging with PET for research purposes is nitrogen-13 (N-13) ammonia. This tracer has a half-life of 10 min and requires a cyclotron on-site to produce it. Although the longer half-life makes N-13 ammonia less efficient for repeated injections, the tracer is more suitable for gating studies.
Pooled analysis of seven PET studies (one study using N-13 ammonia, four using Rb-82 and two using both) including 663 patients thus far showed a high sensitivity of 89 and a specificity of 86% for the detection of CAD.\textsuperscript{29}

An important advantage of PET is the quantification of coronary flow reserve, which allows evaluation of endothelial function. Thus, the technique can be used to detect early atherosclerotic disease activity in patients with elevated risk profiles (e.g. diabetes mellitus or hypercholesterolaemia) but yet without clear significant coronary stenoses,\textsuperscript{31,32} thereby providing an opportunity for monitoring of response to therapy and lifestyle modification.

The main limitations of PET imaging are the need of an on-site (or nearby) cyclotron and the expense of PET, hampering widespread use at present. The duration of a complete PET examination with N-13 ammonia is 100–120 min (rest and stress imaging together), whereas a complete examination with rubidium-82 will take \( \sim 45 \) min (rest and stress imaging).\textsuperscript{33} As with SPECT, the main limitation for the patient is the radiation burden.

**Echocardiography**

Echocardiography is routinely used in daily clinical practice for the analysis of cardiac function as it is relatively easy to perform. Other advantages include the low costs of the examination and minimal patient discomfort.

**Stress echocardiography**

During stress echocardiography, the occurrence of new or worsening wall motion abnormalities during stress indicates the presence of myocardial ischaemia, whereas wall motion abnormalities at rest in general represent infarcted myocardium.\textsuperscript{34} Stress can be induced by exercise, by a vasodilator (for instance, dipyridamole) or by dobutamine. Pooled analysis of 15 studies (\( n = 1849 \) patients), in which exercise echocardiography was used to detect CAD, showed a weighted mean sensitivity of 84% and a weighted mean specificity of 82%.\textsuperscript{35} A meta-analysis of 28 studies (\( n = 2246 \) patients) with dobutamine echocardiography demonstrated a weighted mean sensitivity of 80% and a weighted mean specificity of 84%.\textsuperscript{35} Comparison of exercise stress with dipyridamole stress by means of meta-analysis of eight studies (\( n = 533 \) patients) demonstrated a significantly higher sensitivity for detection of inducible myocardial ischaemia for the former (79 versus 72%, \( P < 0.05 ) . \textsuperscript{36} Specificity, in contrast, was higher for dipyridamole stress echocardiography (92 versus 82%, \( P < 0.05 ) . \) As a result, diagnostic accuracy of both tests appeared to be comparable (77% for dipyridamole versus 80% for exercise stress echocardiography, \( P = \text{NS} ) . \)
Limitations of stress echocardiography mainly include operator dependency and suboptimal image quality due to a poor acoustic window.

**Contrast echocardiography**

The use of intravenous contrast agents allows the assessment of myocardial perfusion with echocardiography. After administration, the microbubbles will reside in the vascular space until they dissolve and can, therefore, be used for evaluation of the microvascular circulation. Recently, a large multicentre trial compared myocardial contrast echocardiography (MCE) with perfusion SPECT imaging for the detection of significant coronary artery stenosis in patients with known or suspected CAD. This study, in 123 patients, demonstrated that the accuracy of MCE is comparable with that of SPECT, both on patient level and on vascular territory level, for the detection of significant stenosis. In addition, intravenous contrast may enhance echocardiographic image quality by improving endocardial delineation. Indeed, significant improvement with contrast in identifying the endocardial borders in comparison with unenhanced fundamental echocardiography was observed by Senior et al. Integration of systolic wall motion abnormalities and perfusion may further enhance the diagnostic value of the test. The duration of a resting echocardiographic examination is normally 20–30 min.

**CMR imaging**

**Cardiac function**

In patients with ischaemic heart disease, the evaluation of global and regional LV function provides important information for patient management, and it has been demonstrated that LVEF is an important prognostic marker in CAD. Owing to its excellent resolution, CMR has been established as a precise and highly reproducible modality for the measurement of LV systolic and diastolic function. In addition, regional wall motion assessed with CMR can be evaluated accurately, which may provide information on myocardial viability. Accordingly, CMR is currently considered to be the gold standard for the assessment of cardiac function. Global and regional LV function can also be assessed during stress with CMR. A frequently used stressor for this purpose is dobutamine. A meta-analysis of 10 studies (n = 654 patients) demonstrated high values for the detection of ischaemia, with a weighted mean sensitivity of 89% and a weighted mean specificity of 84%.

**Myocardial perfusion**

Myocardial perfusion can be evaluated by CMR by continuous data acquisition during the first pass of a bolus of contrast agent. Imaging is repeated during pharmacological stress. Subsequently, ischaemic areas
can be identified as regions of low signal intensity within the myocardium. A pooled analysis of 17 CMR perfusion studies, including 502 patients, revealed a weighted mean sensitivity of 84% and a specificity of 85%.\textsuperscript{35,42–44} Another commonly used technique is delayed contrast enhancement with CMR, which provides information on the extent of scar tissue. Ten to fifteen minutes post-injection of gadolinium-diyethylenetramine pentaacetic acid (DTPA), the contrast will have disappeared in normal myocardium, whereas scar tissue will appear as a hyperenhanced area on the CMR images (Fig. 5). As the technique has a high spatial resolution, distinction between subendocardial and transmural infarctions is possible in contrast to other modalities.\textsuperscript{45}

**Future perspectives**

This review illustrates the role of the different non-invasive imaging techniques for anatomical and functional evaluation of CAD. Initially, first-line evaluation of CAD was performed by means of functional imaging techniques, and the presence or absence of ischaemia served as gatekeeper for invasive coronary angiography. More recently, the emphasis has been shifted to direct visualization of the coronary arteries with non-invasive anatomical imaging techniques. The advantage of the latter is that they allow early detection of atherosclerosis, and thus allow identification of patients who may benefit from further testing as well as from treatment. However, on the basis of anatomical

![Fig. 5 Example of a patient with delayed contrast enhancement on CMR. Panel A: vertical long-axis image with delayed enhancement (white arrows) in patient with prior infero-posterolateral infarction. Panel B: short-axis image with delayed enhancement (white arrows) of the same patient.](image-url)
studies, one cannot determine the presence and extent of ischaemia, and functional testing will remain necessary to decide whether revascularization or medical therapy is indicated.

Integration of non-invasive anatomical imaging appears, therefore, to be most beneficial in patients with an intermediate likelihood for CAD, in which management is often difficult. A potential strategy in these patients may be to first evaluate the presence of atherosclerosis by means of coronary calcium scoring or non-invasive coronary angiography (CT or CMR imaging). In the absence of coronary atherosclerosis, further investigation is not needed and the patient can be discharged safely. However, if atherosclerosis is demonstrated, additional evaluation is warranted to assess the presence of myocardial ischaemia (by means of gated SPECT, PET, stress and/or contrast echocardiography or CMR). If ischaemia are detected, invasive angiography and possibly even intervention are indicated. In contrast, medical therapy and aggressive risk profile modification may be the preferred therapeutic regimen in the case of absence of ischaemia.

A new concept is the integration of various imaging modalities, with PET–CT as the currently most investigated technique. A PET–CT scanner would allow direct combination of anatomical landmarks with functional information, implying that in a patient not only coronary atherosclerosis can be assessed, but also during the same examination the haemodynamic consequences of the atherosclerosis can be determined. However, for daily clinical practice, a combination of MSCT and SPECT would be more appropriate and these combined scanners are currently under development as well.

In conclusion, non-invasive imaging has become increasingly important for the detection of coronary artery stenosis, and it plays a substantial role in the diagnostic and prognostic work up of patients with an intermediate likelihood of CAD. Traditionally, the presence of CAD has been assessed by means of functional techniques, which determine the presence of ischaemia. More recently, non-invasive anatomical imaging has been introduced, allowing detection of atherosclerosis. The expectation is that integration of these different imaging modalities may allow further optimized and more patient-tailored management of patients with known or suspected CAD.

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