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Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Chapter 1

Cardiac Imaging in Coronary Artery Disease: *Differing Modalities*

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Introduction

Coronary artery disease (CAD) remains one of the leading causes of morbidity and mortality worldwide. Moreover, the disease is reaching endemic proportions and will put an enormous strain on health care economics in the near future. Non-invasive testing is important to exclude CAD with a high certainty on the one hand, and to detect CAD with its functional consequences at an early stage, to guide optimal patient management, on the other hand. For these purposes, non-invasive imaging techniques have been developed and used extensively over the last years. Currently, the main focus of non-invasive imaging for diagnosis of CAD is twofold: 1. **functional imaging**, assessing the hemodynamic consequences of obstructive CAD, and 2. **anatomical imaging**, visualizing non-invasively, the coronary artery tree. For functional imaging, nuclear cardiology, stress echocardiography and magnetic resonance imaging (MRI) are used, whereas for anatomical imaging or non-invasive angiography, MRI, multi-slice CT (MSCT) and electron beam CT (EBCT) are used. The aim of this chapter is to update the reader on the current status of non-invasive imaging, with a special focus on functional imaging versus anatomical imaging for the detection of CAD. The accuracies of the different imaging modalities are illustrated using pooled analyses of the available literature data when available.

Functional Imaging

What information does functional imaging provide?

The hallmark of functional imaging is the detection of CAD by assessing the hemodynamical consequences of CAD rather than by direct visualization of the coronary arteries. For this purpose, regional perfusion or wall motion abnormalities are induced (or worsened) during stress, reflecting the presence of stress-induced ischemia. Ischemia induction is based on the principle that although resting myocardial blood flow in regions supplied by stenotic coronary arteries is preserved, the increased flow demand during stress cannot be met, resulting in a sequence of events referred to as “the ischemic cascade”¹. Initially perfusion abnormalities are induced, followed by diastolic and (at a later stage) systolic dysfunction; only at the very end of the cascade, ECG changes and angina occur (Figure 1).

Accordingly, the occurrence of perfusion abnormalities during stress may be more sensitive for the detection of CAD than the induction of systolic dysfunction (wall motion abnormalities).

Currently, functional imaging can be performed using (gated) SPECT or PET, (contrast) stress echocardiography and MRI; all techniques allow integrated assessment of perfusion and function, at rest and after stress and are used clinically according to local availability and expertise.

Types of stress

An increased demand can be achieved through physical (bicycle or treadmill) exercise, or (in patients unable to exercise), pharmacological stress can be applied including adrenergic stimulation

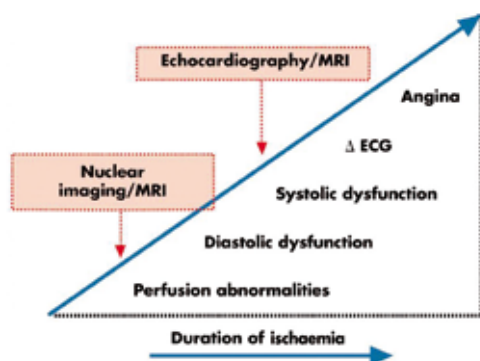


Figure 1. The ischemic cascade represents the sequence of pathophysiological events following ischemia.

and vasodilation. Dobutamine (a beta-1-specific agonist) increases heart-rate, contractility and arterial blood pressure, resulting in increased myocardial oxygen demand. The vasodilators include dipyridamole and adenosine. Adenosine is a direct vasodilator, while dipyridamole inhibits cellular uptake and breakdown of adenosine. Dipyridamole therefore has a slower onset, while its effect lasts longer. Aminophylline can be used as antidote.

Safety of all pharmacological stressors has been investigated extensively and although continuous patient monitoring is required, severe complications are rare ^{2,3}.

Which modalities are available for functional imaging?

SPECT, assessment of perfusion

Most experience for assessment of perfusion in daily clinical practice has been obtained with SPECT.

Three radiopharmaceuticals are used: thallium-201, technetium-99m sestamibi and technetium-99m

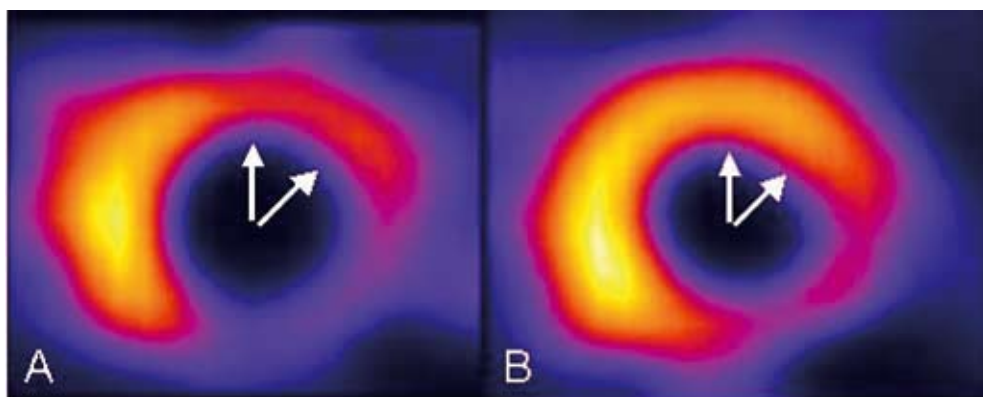


Figure 2. Example of a reversible defect on technetium-99m tetrofosmin SPECT. Panels A and B show short-axis slices following stress and at rest, respectively. A reversible defect is present in the anterior and antero-lateral regions (white arrows), illustrating stress-inducible ischemia. A fixed perfusion defect, most likely representing scar tissue is present in the postero-lateral and inferior region.

tetrofosmin. Currently, the technetium-99m labeled tracers are preferred for their higher photon energy resulting in less attenuation artefacts. Two sets of images are obtained: after stress and at rest. In general, reversible and irreversible defects are considered indicative of CAD. While reversible (stress-induced) defects reflect ischemia, irreversible (fixed) defects mainly represent infarcted myocardium (Figure 2).

Images are interpreted visually or using automated quantification. For segmentation of the left ventricle (LV), a 17-segment model is developed, that can be applied to all functional imaging modalities⁴. To assess the diagnostic accuracy of SPECT for detection of CAD, Underwood et al pooled 79 studies (n=8964 patients) showing a weighted mean sensitivity and specificity of 86% and 74% (Figure 3)⁵. The lower specificity of SPECT may be (partially) attributable to referral bias, i.e. among patients with normal SPECT studies, only those with a high suspicion for CAD are referred for coronary angiography. To overcome this problem, the normalcy rate has been introduced, which is the percentage of normal SPECT studies in a population with a low likelihood of CAD. Pooled analysis of 10 studies (n=543 patients) showed a normalcy rate of 89%.⁵

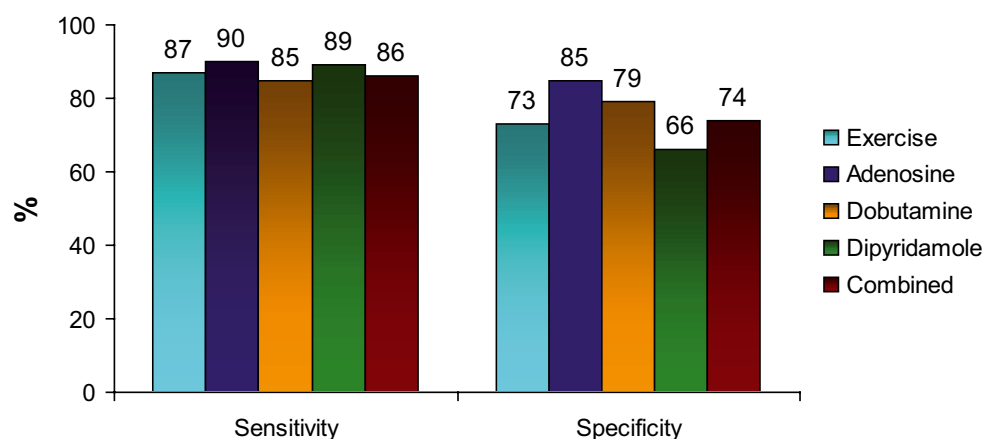


Figure 3. Sensitivities and specificities of SPECT imaging for the detection of CAD, using different stressors (Based on reference⁵).

SPECT, assessment of systolic function

The introduction of ECG-gated SPECT imaging, has allowed assessment of global and regional LV function in addition to perfusion. Direct comparisons between gated SPECT and MRI (or echocardiography) showed excellent correlations for assessment of LV ejection fraction, volumes and regional wall motion^{6,7}. Addition of these systolic function parameters has improved diagnostic accuracy. In particular, artefacts caused by soft tissue attenuation, could be unmasked by the demonstration of normal wall motion. This resulted in a substantial reduction of false-positive test results⁸. Integration of perfusion and systolic function by SPECT resulted in a significant reduction (from 31% to 10%) of inconclusive tests, with an increase in normalcy rate from 74% to 93%⁹.

Echocardiography, assessment of systolic function

Stress echocardiography is readily available for the routine evaluation of (stress-inducible) wall motion abnormalities (Figure 4); both resting and stress-induced (or worsened) wall motion abnormalities are indicative of CAD. While stress-induced (or worsened) wall motion abnormalities reflect ischemia, resting wall motion abnormalities mainly represent infarcted myocardium.

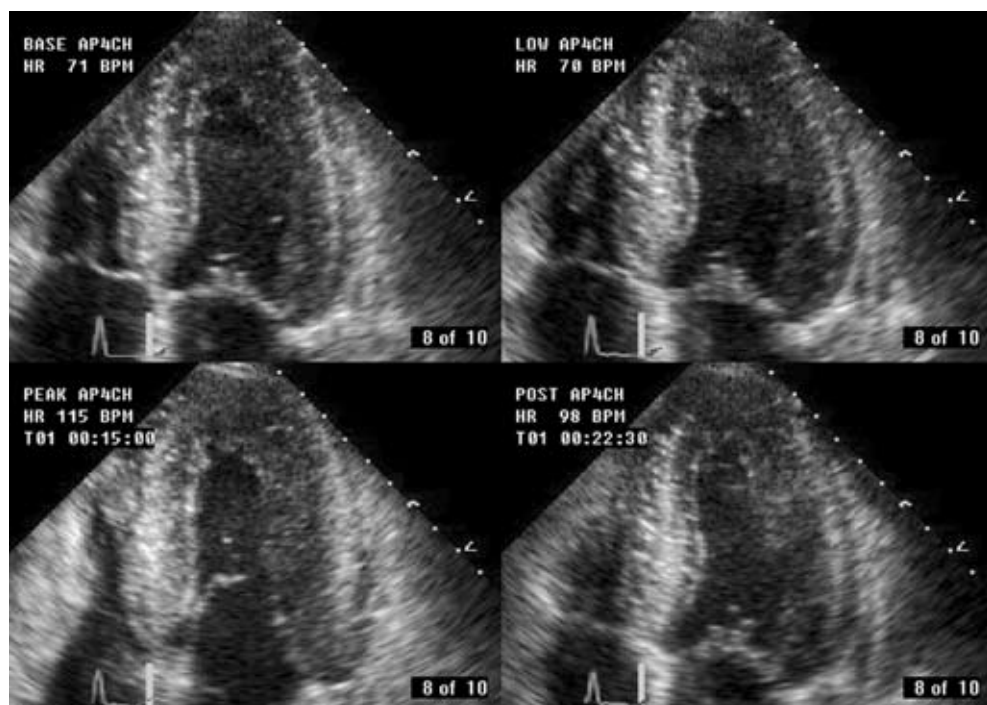


Figure 4. Example of a stress-induced wall motion abnormality on dobutamine echocardiography. Panels A, B, C and D are obtained during rest, low- (10 $\mu\text{g/kg/min}$) and high-dose dobutamine (40 $\mu\text{g/kg/min}$) and recovery. In the septal region (white arrow), normal wall motion is present at rest and during low-dose dobutamine infusion, whereas dyskinesia is induced at high-dose dobutamine.

A total of 15 studies ($n=1849$ patients) used exercise echocardiography to detect CAD, with a weighted mean sensitivity and specificity of 84% and 82%.¹⁰ Pooled data from 28 dobutamine echocardiography studies ($n=2246$ patients), showed a weighted mean sensitivity and specificity of 80% and 84% to detect CAD.¹⁰ The accuracies for the different forms of stress echocardiography are summarized in Figure 5. It has been demonstrated that continuation of beta-blockers reduced sensitivity, which could be improved by addition of atropine. Also, sensitivity increased in parallel to the number of diseased vessels, from 74% for 1-vessel disease to 92% for 3-vessel disease. Disadvantages of stress echocardiography in general include a suboptimal acoustic window in up to 25% of patients and drop-out of the anterior and lateral walls. Improved endocardial border delineation can be obtained by using second harmonic imaging and administration of intravenous contrast agents.

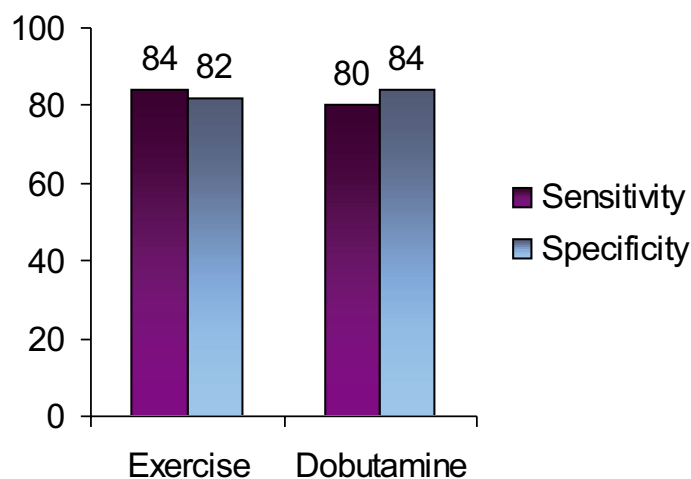


Figure 5. Diagnostic accuracy of stress (exercise and dobutamine) echocardiography (data based on reference ¹⁰).

Echocardiography, assessment of perfusion

At the same time the use of contrast agents has allowed the assessment of myocardial perfusion. After contrast injection, the micro-bubbles remain in the vascular space until they dissolve, and thus reflect the microvascular circulation. Accordingly, their relative concentrations in different regions of the myocardium (as measured by signal intensity) reflect the relative myocardial blood volume in those regions. Similar to SPECT, resting perfusion defects suggest infarcted myocardium, whereas stress-induced perfusion defects indicate ischemia. Currently, many modifications of the technology have been introduced and real-time assessment of perfusion by contrast echocardiography is now possible ¹¹.

Recent studies from experienced centers showed an excellent agreement between SPECT and myocardial contrast echocardiography for detection of perfusion abnormalities, with a comparable sensitivity/specificity for the detection of CAD ^{12,13}. In a head-to-head comparison, Jucquois et al ¹⁴ demonstrated an agreement of 62% between SPECT and contrast echocardiography for detection of perfusion defects; the disagreement between the 2 techniques was related to attenuation artefacts and when these segments were excluded, the concordance improved to 82%.

The integration of assessment of perfusion and function by contrast echocardiography performed at rest and after stress should provide optimal information on the detection of CAD. Moir et al recently performed myocardial contrast echocardiography in addition to combined dipyridamole-exercise echocardiography in 85 patients ¹⁵. In 70 of these patients, data could be compared to conventional coronary angiography. Sensitivity for the detection of CAD was significantly improved by the addition of contrast from 74% to 91%; specificity on the other had showed a (non-significant) decrease from 81% to 70%. Pooled analysis of the 7 currently available studies (n=245 patients) on the additive value of perfusion imaging with contrast to standard wall motion imaging showed similar results: the weighted mean sensitivity for detection of CAD was 89% with a specificity of 63% ¹⁵⁻²¹.

MRI, assessment of perfusion

A relatively new technique to evaluate myocardial perfusion is MRI. For this purpose, 5-8 slices in the short-axis orientation are imaged during the first pass of a bolus of a contrast agent. Imaging is repeated during pharmacological stress. The applied contrast agent, gadolinium, temporarily changes the T1-relaxation time and thereby increases the signal intensity of the perfused myocardium. In contrast, ischemic regions are identified as areas with little or reduced signal intensity (Figure 6).

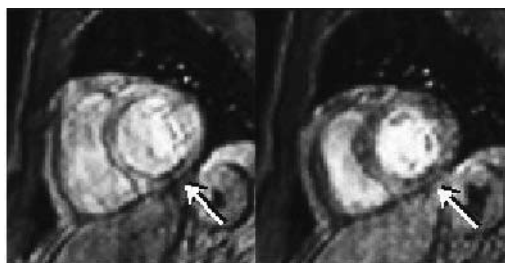


Figure 6. MR perfusion images in respectively rest (Panel A) and stress (Panel B) showing a fixed perfusion defect in the inferior wall (white arrows). Images were acquired using a breath hold sensitivity encoding imaging technique during the first pass of an intravenously administered bolus of Gadolinium contrast agent.

Pooling of 17 MRI perfusion studies (n=502 patients, using either dipyridamole or adenosine stress) revealed a weighted mean sensitivity and specificity of 84% and 85% (Figure 7)^{10;22-24}. The high spatial resolution (approximately 2 mm), enables distinction between subendocardial and transmural perfusion defects. This is an important advantage over SPECT imaging, since the occurrence of subendocardial perfusion defects may indicate compromised blood flow at an early stage.

For clinical routine, images are evaluated visually, although semi-quantitative assessment is possible by calculation of the myocardial perfusion reserve index^{25;26}. In the future, absolute quantification of myocardial perfusion may be allowed by the use of new intravascular contrast agents. At present however, quantitative analysis is still time-consuming and in order to fully exploit this modality in standard clinical routine, automated quantification algorithms are needed.

MRI, assessment of systolic function

In addition to myocardial perfusion, global and regional systolic LV function can also be obtained with MRI. The most widely used steady-state free precession technique allows clear identification of endocardial borders due to a high blood pool signal. In addition, the tomographic approach allows measurement of volumes without geometric assumptions, resulting in accurate measurements in severely distorted ventricles as well. Global and regional LV function can be obtained at rest and during stress (mainly using dobutamine). Pooled data of 10 dobutamine MRI studies (n=654 patients) revealed a weighted mean sensitivity and specificity of 89% and 84% (Figure 7)^{10;22}.

The excellent endocardial-blood pool contrast is in particular beneficial for patients with poor echocardiographic windows. Unfortunately, MRI is still limited to highly specialized centers and

acquisition protocols are still time consuming, making the technique currently unsuitable for evaluation of larger populations. No MRI studies with integration of systolic wall motion and perfusion to detect CAD are currently available.

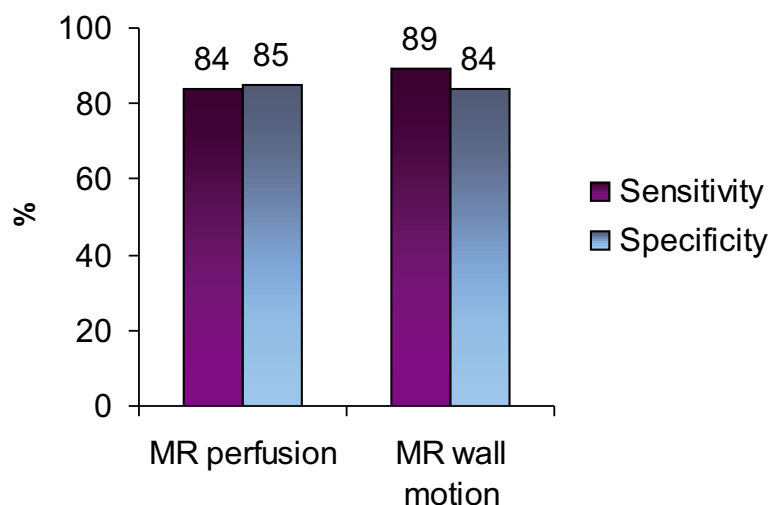


Figure 7. Diagnostic accuracy of perfusion and wall motion imaging MRI (data are based on references ^{10,22-24}). For the perfusion studies, adenosine or dipyridamole was used, while dobutamine was administered during the wall motion studies.

Anatomical Imaging

Why is anatomical imaging needed?

Although a safe and accurate evaluation of patients with known or suspected CAD is offered by **functional imaging**, in a substantial number of patients **anatomical imaging** is needed. First, in patients with abnormal stress tests, direct visualization of the coronary tree is still required for the definite diagnosis of CAD. Moreover, decisions on treatment strategy, e.g. whether the observed coronary lesions will be treated conservatively (medically) or more aggressively by means of PCI or CABG are based to a large extent on the findings of conventional coronary angiography. Also, in certain subpopulations, e.g. diabetes, functional imaging may be less reliable. In these patients, diffuse atherosclerosis in all major epicardial vessels is frequently present, resulting in the absence of detectable perfusion abnormalities. Considering the fact that if CAD is present, prognosis is substantially worse compared to non-diabetic individuals, knowledge of coronary anatomy is needed. Thus, besides detection of hemodynamical consequences, direct visualization of the coronary anatomy is frequently needed.

What is the current gold standard for anatomical imaging?

At present, conventional X-ray angiography with selective contrast injection through cardiac catheterization remains the reference standard for the evaluation of the coronary arteries. Both spatial (0.2 mm) and temporal resolution (5 ms) of the technique are extremely high. In addition, the degree of luminal narrowing can be precisely measured using quantitative coronary angiography. Also, when during the diagnostic procedure the presence of one or more significant lesions is confirmed, direct intervention is possible.

Currently, approximately 3000 invasive diagnostic procedures per million inhabitants have been performed in Europe in 2001, which resulted in PTCA in only one out of three²⁷. The development of non-invasive imaging of the coronary arteries would potentially facilitate the access to anatomical imaging and expand the indications for revascularization.

What are the available modalities for non-invasive anatomical imaging?

Currently, 3 techniques are being developed for non-invasive angiography, MRI, MSCT and EBCT. Although results are promising, all techniques still have shortcomings and limitations, hampering implementation in routine clinical practice. Since the coronary arteries are small, tortuous and show rapid movement during cardiac cycle, demands on spatial and temporal resolution of the techniques are tremendous. However, all techniques are developing at a rapid pace and as a result, image quality and diagnostic accuracy are continuously improving.

Non-invasive angiography with MRI

More than 10 years ago, the first results of non-invasive angiography were reported by Manning and colleagues²⁸. The authors performed a comparison between 2D MRI and conventional angiography in 39 patients and observed a sensitivity and specificity of 90% and 92%, respectively. With these first generation techniques, data were acquired during consecutive breath holds, requiring substantial patient cooperation. To enable free breathing, navigator techniques, that allow real-time monitoring of diaphragm motion, have been developed. In combination with the development of 3-dimensional acquisition techniques, superior visualization of coronary anatomy was achieved. In Figure 8, examples of non-invasive coronary angiography with 3D MR acquisition techniques are provided.

Pooled data from 28 studies (n=903 patients) directly comparing MRI with invasive angiography showed a weighted mean sensitivity of 72% with a specificity of 87% (Figure 9).²⁹ However, the percentage of interpretable segments is still insufficient and exclusion of up to 30% of all segments has been reported, even with newer acquisition techniques. Thus, full coverage of the coronary arteries within a reasonable amount of time still cannot be achieved. Future developments in the area of coronary MRA, including higher field strengths (3T) and improved contrast techniques, such as balanced steady-state-free-precession techniques and the development of blood pool

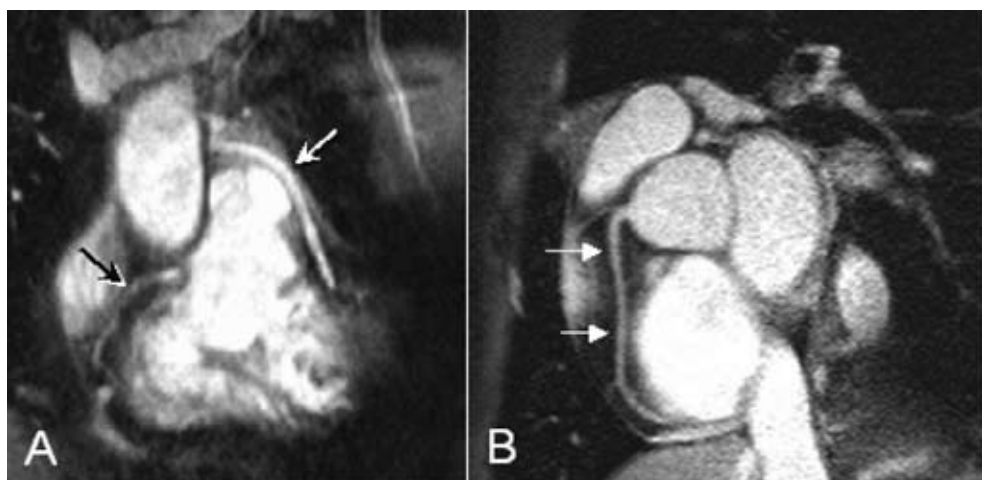


Figure 8. Non-invasive coronary angiography with MRI. In Panel A, a native right coronary artery (black arrow) and a venous coronary bypass (white arrow) on the left anterior descending coronary artery can be observed. In contrast, Panel B depicts the right coronary artery (white arrows) of a healthy volunteer. Images were acquired with a 1.5 T system, using T_2 -preparation for background suppression during respiratory gating.

contrast agents, will improve diagnostic accuracy. Moreover, extensive research is directed towards assessment of plaque composition as well as assessment of coronary flow, which may potentially enable the technique to provide a comprehensive evaluation of both the presence and extent, as well as the functional significance of CAD.

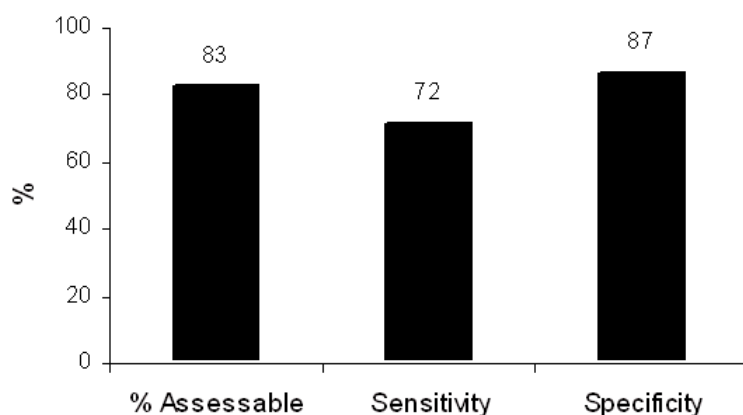


Figure 9. Diagnostic accuracy of non-invasive coronary angiography with MRI in the detection of significant stenoses (data based on reference ²⁹).

Non-invasive angiography with MSCT

More recently, MSCT has emerged as a potential modality for non-invasive angiography. Initial studies with 4-slice technology showed promising results, with sensitivities and specificities ranging from 66% to 90% and from 71% to 99%, respectively²⁹. However, the technique was still hampered by the high percentage of segments (approximately 25%) with non-diagnostic quality. Modern systems have an X-ray gantry rotation time of 400 ms or less while data are acquired using 16 or more parallel detectors with sub-millimeter collimation. At present, 11 studies with 16-slice technology have been reported²⁹. As expected, considerably more segments were available for evaluation, approximately 96% of segments. Furthermore, an increase in sensitivity from (on average) 80% to 88% could also be observed with no loss in specificity (Figure 10). With 64-slice systems that have recently become available, both the percentage evaluable segments and sensitivity are expected to improve further.

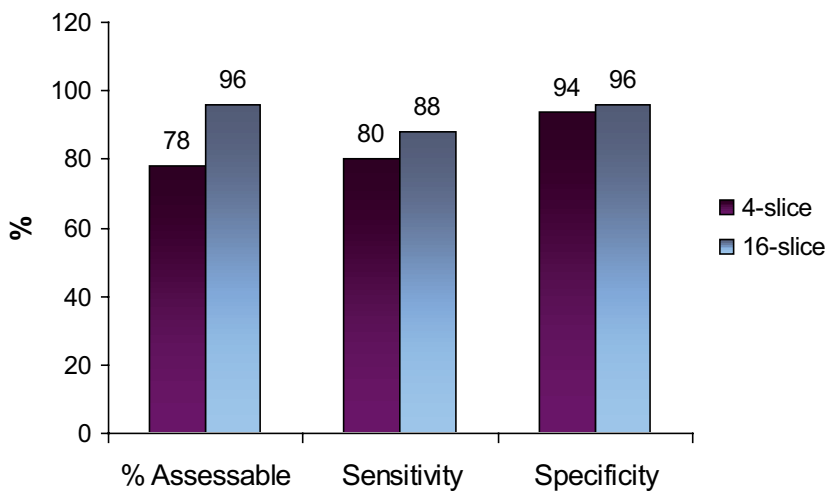


Figure 10. Diagnostic accuracy of non-invasive coronary angiography with 4- and 16-slice MSCT in the detection of significant stenoses (data based on reference²⁹).

Since data are acquired during consecutive heartbeats, a stable heart rate is important in order to obtain good image quality. Similar to MRI, the technique has therefore limited value in patients with atrial fibrillation or frequent extra-systolic contractions, although for the latter raw data can sometimes be manually corrected. Other contra-indications to MSCT include renal failure or pregnancy due to the administration of contrast agent and the use of ionizing radiation, respectively. Moreover, the radiation dose associated with a MSCT examination is still considerably high and remains an important limitation of the technique. To reduce radiation dose, prospective X-ray tube modulation or more dedicated filtering may be applied while other dose reduction strategies are currently investigated.

Non-invasive angiography with EBCT

The first experiences with coronary angiography with EBCT were described in 1995³⁰. Instead of a mechanically rotating tube, X-rays are created through an electron beam that is guided along a 210° tungsten target ring in the gantry. As a result, a high-resolution image is acquired in 50 -100 ms. The acquisition of serial overlapping cross-sectional images with a 1.5 or 3.0 mm slice thickness is performed during the administration of an iodinated contrast agent, using prospective ECG triggering. To cover the whole heart, 40 to 50 slices are necessary, typically requiring a breath hold of 30 to 40 seconds, depending on the heart rate. Pooled analysis of the 10 available studies (n=583 patients) comparing contrast-enhanced EBCT angiography with conventional angiography demonstrated a weighted mean sensitivity and specificity of 87% and 91% respectively³¹; 16% of the coronary arteries were non-interpretable (Figure 11). Similar to other non-invasive coronary angiography techniques, distal coronary segments are relatively more difficult to image, while coronary artery motion and breathing artifacts also frequently occur.

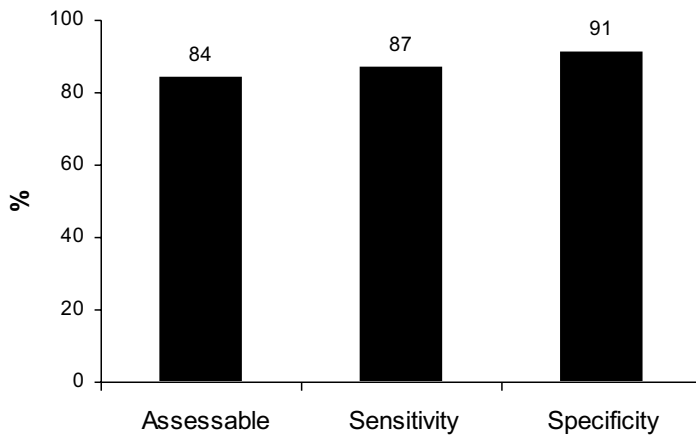


Figure 11. Image quality and diagnostic accuracy of EBCT (Data based on reference³¹).

Coronary artery calcium scoring

Another, more frequently performed application of EBCT is the quantification of calcium in the coronary arteries. The presence of calcium serves as a marker of atherosclerosis. The absence of calcium virtually excludes atherosclerosis, and no further analysis is needed. This is also supported by the very low rate of cardiac events in patients without calcium on EBCT; Raggi et al³² demonstrated in 4800 patients without diabetes and no coronary calcium that the 5-year survival was 99.4%. By multivariate analysis, the presence of coronary calcium contributed to the prediction of all cause mortality in 9474 asymptomatic and non-diabetic subjects to the same extent as age, hyperlipidemia, hypertension and active smoking. Moreover, Berman et al³³ showed that <1% of patients with minimal coronary calcium had ischemia on SPECT imaging.

However, the presence of coronary calcium only indicates atherosclerosis in general and requires additional evaluation. In particular, no relation between the extent of coronary calcium and stenosis severity has been shown.³¹

Keypoints

1. In the presence of a significant coronary artery stenosis, a sequence of events called the “ischemic cascade” occurs during stress: first perfusion abnormalities occur, followed by wall motion abnormalities, while ECG changes and angina occur at a later stage.
2. Non-invasive imaging to assess CAD can be divided into **functional imaging** and **anatomical imaging**.
3. Functional imaging aims at assessment of the hemodynamic consequences of obstructive CAD; the available techniques are nuclear imaging (mainly SPECT), stress echocardiography (with the optional use of intravenous contrast agents) and MRI.
4. Currently, all three **functional imaging** modalities allow *comprehensive* evaluation including assessment of both perfusion and wall motion.
5. For non-invasive **anatomical imaging**, or non-invasive coronary angiography, MRI, MSCT and EBCT are used. These modalities do not yet assess the hemodynamic consequences of CAD.

Conclusion and outline of the thesis

As discussed in this chapter, the emphasis of non-invasive imaging has traditionally been on functional imaging (assessing the hemodynamic consequences of obstructive CAD, i.e. ischemia). Over the past decades, non-invasive imaging for the detection of CAD has mainly relied on SPECT and stress echocardiography, functional imaging techniques to assess perfusion or wall motion abnormalities (as markers of CAD) respectively. Over time, these techniques were considered **complementary**, rather than **competitive**, since they provided different information. At present however, both SPECT and echocardiography have developed into **comprehensive** imaging techniques, and each can assess both perfusion and wall motion. Similarly, MRI can also assess both perfusion and wall motion. Still, for proper patient management, knowledge on coronary anatomy is frequently needed and patients are subsequently referred for invasive angiography.

With the more recent introduction of non-invasive coronary angiography, emphasis has shifted to anatomic imaging. In particular, initial results with MSCT have been promising. However, prior to optimal integration of this novel technique within daily clinical practice, several issues need to be considered.

The aim of this thesis was to describe the value and potential role of MSCT within the multiple modalities that are available for evaluation of patients with suspected CAD.

Initially, this new technique, allowing non-invasive coronary angiography, has been validated against conventional coronary angiography, as described in Chapters 2–4 in **Part I**. In Chapter 2, data acquisition, post-processing and potential applications of MSCT are outlined. The diagnostic accuracy of 16- and 64-slice MSCT in detecting significant coronary stenoses is evaluated in Chapters 3 and 4, respectively.

In Chapter 5 the diagnostic accuracy of MSCT was compared to MRI based on a meta-analysis of the available literature. Subsequently, in **Part II**, the potential value of non-invasive imaging with MSCT and MRI was investigated in certain subset of patients, in order to define potential candidates for MSCT in more detail. Populations that were studied included patients with risk factors (Chapters 6-8) and patients with previous revascularization (Chapters 9-12).

While MSCT coronary angiography has been suggested as an alternative first-line imaging modality to rule out CAD prior to more invasive procedures, comparisons to the traditionally used non-invasive first-line techniques were not available. The purpose of **Part III** therefore, was to evaluate the relationship between anatomical observations on MSCT, namely atherosclerosis, and functional consequences on MPI, namely ischemia. In Chapter 13, an update of the various non-invasive modalities, including both anatomical as well as functional modalities, is provided. In addition, a potential algorithm for integration of these modalities is proposed, which is further discussed in Chapter 15. The relation between MSCT and functional imaging is investigated in Chapters 14, 16, and 17.

In **Part IV**, the potential of atherosclerosis imaging with MSCT was further explored. First, differences in plaque patterns between various clinical presentations were evaluated in Chapters 18 and 19. The potential prognostic value of MSCT plaque observations was tested in Chapter 20.

Finally, in **Part V**, non-coronary applications are evaluated, including quantification of infarct transmural (Chapter 21), analysis of resting LV function and perfusion (Chapters 22 and 23) and imaging of the cardiac venous system (Chapter 24).

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