Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Part III

Anatomical versus Functional Imaging in the Evaluation of Coronary Artery Disease

Chapter 13

Diagnostic and Prognostic Value of Non-Invasive Imaging in Known or Suspected Coronary Artery Disease

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Eur J Nucl Med Mol Imaging 2006; 33: 93-104

Abstract

The role of non-invasive imaging techniques in the evaluation of patients with suspected or known coronary artery disease (CAD) has increased exponentially over the past decade. The traditionally available imaging modalities, including nuclear imaging, stress echocardiography and magnetic resonance imaging (MRI), relied on detection of CAD by visualization of its functional consequences (i.e. ischemia). However, at present, extensive research is invested in the development of non-invasive anatomical imaging using computed tomography (CT) or MRI to allow detection of (significant) atherosclerosis, eventually at a pre-clinical stage.

In addition to establishing the presence of or excluding CAD, identification of patients at high risk for cardiac events is of paramount importance to determine post-test management and for this purpose the majority of non-invasive imaging tests can also be used. The aim of the present chapter is to provide an overview of the available non-invasive imaging modalities and their merits for the diagnostic and prognostic work-up in patients with suspected or known CAD.

Introduction

In the evaluation of patients with suspected or known coronary artery disease (CAD), the role of non-invasive imaging techniques has increased exponentially over the past decade. The traditionally available imaging modalities relied on identification of the presence of significant coronary artery stenoses, by visualization of their functional consequences (i.e. ischemia), reflected by an induction of myocardial perfusion or systolic wall motion abnormalities following stress. For this purpose, nuclear imaging techniques, stress echocardiography and magnetic resonance imaging (MRI) are currently employed. Although these modalities permit reliable detection of ischemia, the presence of (significant) atherosclerosis in the absence of a flow-limiting stenosis is not detectable. At present, extensive research is invested in the development of non-invasive anatomical imaging, e.g. non-invasive assessment of coronary artery calcium or even non-invasive coronary angiography using computed tomography (CT) or MRI. With these techniques, the presence of atherosclerosis rather than ischemia is being evaluated.
Besides the detection or exclusion of CAD (***diagnosis***), identification of patients at high risk for adverse events (***prognosis***) is crucial to determine post-test management and to select those patients who may benefit from revascularization. Indeed, the non-invasive imaging tests provide not only diagnostic but also powerful prognostic information. The purpose of this review is to provide an overview of the available non-invasive imaging modalities and their merits in the diagnosis and prognosis in patients with suspected or known CAD.

Diagnosis of coronary artery disease

Detection of atherosclerosis

Although detection of ischemia provides a reliable evaluation of patients with known or suspected CAD, the recent development of non-invasive imaging of coronary anatomy has increased the interest in detection of atherosclerosis in addition to ischemia. In particular, assessment of diffuse atherosclerosis without ischemia may target assessment of preclinical disease. For this purpose, evaluation of coronary artery calcium by CT techniques has attracted substantial attention, and more recent technological developments have resulted in the possibility to perform non-invasive coronary angiography.
Currently, non-invasive angiography is feasible with MRI, multi-slice CT (MSCT) and electron beam computed tomography (EBCT). Since the coronary arteries are small, tortuous and move substantially during the cardiac cycle, imaging remains technically challenging. As a result, all techniques still have shortcomings and limitations, but with the rapid technical advances, image quality and diagnostic accuracy are continuously improving. Besides non-invasive angiography, these techniques may in the future also allow assessment of plaque composition [1].

Coronary artery calcium scoring

EBCT and MSCT allow non-invasive detection and quantification of coronary artery calcium. In Figure 1, examples of coronary calcium imaging with MSCT are shown. Both EBCT and MSCT provide similar measures of coronary artery calcium but the majority of data has been obtained with EBCT, which has a lower radiation dose and superior reproducibility. The Agatston score is the most widely applied technique for quantification of coronary artery calcium [2]. Although the presence of coronary artery calcium is closely correlated with the total atherosclerotic burden, it is not predictive of significant coronary stenoses and it is not site-specific, meaning that calcified segments are not necessarily stenosed, and the reverse [3].

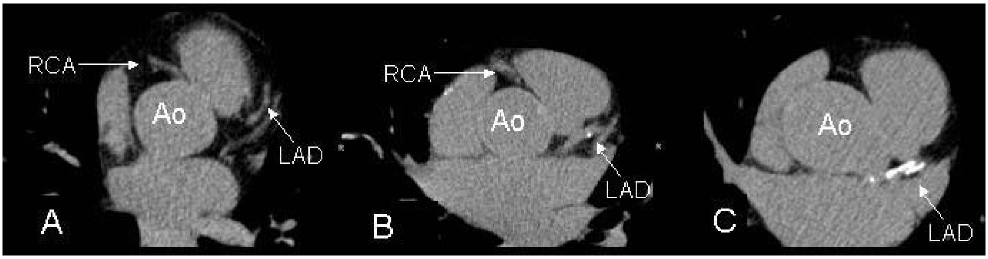

Figure 1. Single-level MSCT calcium scans of patients with respectively no (Panel A), minor (Panel B) and extensive (Panel C) coronary calcifications. Coronary calcifications are identified as regions with high signal intensity, thus appearing as intensely white structures on the MSCT images.
Abbreviations: Ao: Aorta, LAD: left anterior descending coronary artery, RCA: right coronary artery.

Also, non-calcified plaques with a low X-ray density are not detected by coronary artery calcium imaging. However, an approximate of the total atherosclerotic plaque burden is provided and thus the likelihood of having focally obstructive CAD increases in parallel to the coronary artery calcium score [4].

Non-invasive coronary angiography

Magnetic resonance imaging. With the first generation of MR coronary angiography techniques, only one 2D image was acquired per breath-hold, requiring a substantial number of consecutive breath-holds. Accordingly, the clinical applicability was limited [5]. Superior image quality was achieved by 3D imaging, while real-time monitoring of diaphragm motion (respiratory navigator-gating) has enabled data acquisition during free breathing. A pooled analysis of 28 studies (n=903 patients) comparing MRI with invasive angiography as the standard demonstrated a weighted mean sensitivity of 72% with a specificity of 87% [6]. However, the individual studies show a wide variation in diagnostic accuracy and only 1 multi-center study has been reported thus far [7]. In addition, MRI techniques are still hampered by the relatively long acquisition times, and a substantial percentage of segments remains uninterpretable (Figure 2). Improvement of image quality and diagnostic accuracy is anticipated with the introduction of 3Tesla systems and newer acquisition protocols, including balanced steady-state-free-precession techniques and the improvement of blood pool contrast agents.

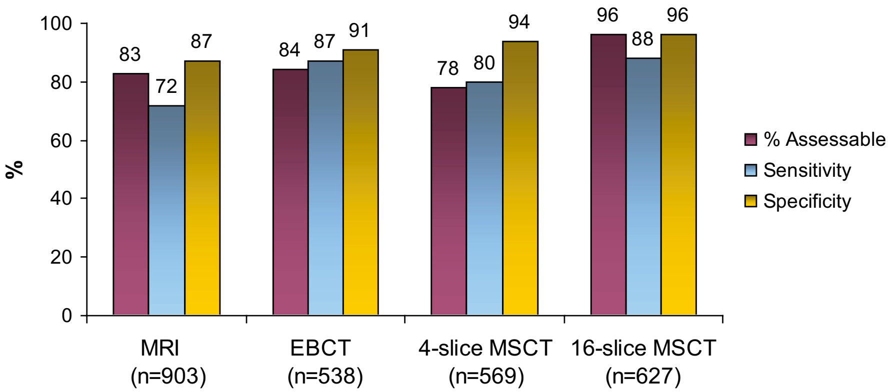

Figure 2. Diagnostic accuracies of the different non-invasive coronary angiography techniques, based on references [6;8].

Electron beam computed tomography. During EBCT, X-rays are created through an electron beam that is guided along a 210° tungsten target ring in the gantry. As a result, images are acquired with high temporal resolution (50-100 ms, depending on the scanner mode used). The acquisition of serial overlapping cross-sectional images with a 1.5 or 3.0 mm slice thickness is performed 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.

A recently published pooled analysis of 10 studies with a total of 538 patients showed a weighted mean sensitivity and specificity of 87% and 91% to detect CAD with EBCT as compared to invasive angiography (Figure 2) [8]. High percentages of uninterpretable segments were consistently observed, with exclusion of approximately 20% of segments from analysis. Another major limitation is the presence of extensive coronary calcifications that interfere with stenosis assessment and lead to overestimation of the degree of luminal narrowing. Motion artifacts also frequently occur, since prospective triggering is used, which does not allow reconstruction of data at other phases of the cardiac cycle. Consequently, EBCT is felt to be not yet robust enough to justify its implementation in clinical routine.

Multi-slice computed tomography. In the late 1990s, MSCT systems were introduced allowing the acquisition of multiple (4) slices instead of 1 slice in a single gantry rotation, thereby enabling CT systems to visualize the coronary arteries. Similar to EBCT, administration of iodinated contrast agent is needed. The initial results with the 4-slice systems were promising, although 20% of coronary segments had to be excluded from analysis due to non-diagnostic quality [6]. Substantial improvement was achieved by the introduction of 16-slice scanners with submillimeter collimation as well as faster rotation times. At present, 11 studies (681 patients) have reported on the accuracy of 16-slice MSCT in comparison to conventional coronary angiography [6]. On average, an increase in sensitivity from 80% (4-slice systems) to 88% (16-slice systems) was noted, with no loss in specificity. Furthermore, more complete coverage of the coronary tree was achieved, with an average of 96% of coronary segments showing sufficient image quality to allow interpretation. Overall diagnostic accuracy and percentage interpretable segments with MSCT are depicted in Figure 2. In general, the specificity of MSCT is extremely high, suggesting that accurate exclusion of CAD can be achieved. However, no large studies have targeted low prevalence patient groups thus far. Further refinement of the technique may be achieved with the recently introduced 64-slice systems, of which an example is provided in Figure 3**.** Despite these encouraging results the technique has still several limitations. The radiation exposure during MSCT examination is in the range of 9-12 mSv, and refinements of imaging protocols are warranted to lower the radiation exposure. In addition, the reported results depend largely on patient selection, with a substantially lower accuracy in patients with higher heart rates or arrhythmias due to motion artifacts [9]. To circumvent this problem, routine administration of beta-blocking medication is currently performed in many centers. Image quality may also be degraded in patients with severe CAD due to the presence of extensive calcifications which potentially limit precise assessment of the stenosis severity [10].

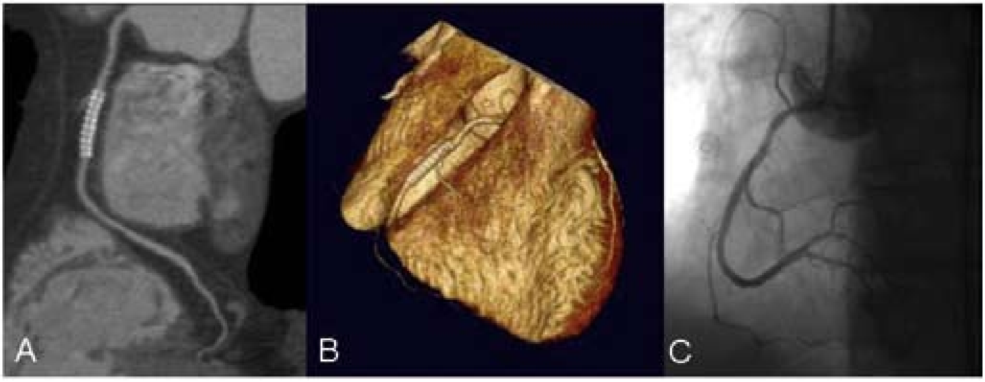

Figure 3. Example of non-invasive coronary angiography with 64-slice MSCT. In Panel A, a curved multiplanar reconstruction of the right coronary artery with stent placement is shown. No significant stenoses are observed. In Panel B, a 3D volume-rendered reconstruction is depicted, showing the right coronary artery and its side-branches. Findings were confirmed by invasive coronary angiography (Panel C).

However, whether elevated calcium scores should be used as an indication to defer MSCT coronary angiography remains debatable with recent research suggesting unaffected diagnostic accuracy even in the presence of high coronary calcification scores [11]. Accordingly, further investigations are needed to determine which patient groups may ultimately benefit the most from non-invasive coronary angiography with MSCT [12].

Detection of ischemia

In the presence of a flow-limiting stenosis, resting myocardial blood flow is still preserved, whereas increased myocardial oxygen demand will result in a demand/supply mismatch, leading to inducible myocardial ischemia. As a result, a sequence of events is initiated, which is referred to as the ischemic cascade [13]. Perfusion abnormalities are induced at an early stage, followed by diastolic and systolic left ventricular (LV) dysfunction. ECG changes and angina only occur at the end of the cascade.

Various imaging modalities are available to demonstrate these early changes during ischemia, including (gated) SPECT or PET, (contrast) stress echocardiography and MRI; local availability and expertise mainly determine which technique is used. Stress can be achieved using physical (bicycle or treadmill) exercise, or pharmacological stress (using dobutamine or vasodilators including dipyridamole and adenosine).

Nuclear imaging techniques

Single photon emission computed tomography. The most widely available nuclear technique to assess myocardial perfusion is SPECT using thallium-201, technetium-99m sestamibi or technetium-99m tetrofosmin. Average sensitivity and specificity, based on a pooled analysis of 79 studies with 8964 patients included, are 86% and 74%, respectively [14]. Although the technique is very sensitive, as perfusion abnormalities occur early in the ischemic cascade, specificity is lower, as shown in Figure 4**.** This may (in part) be related to post-test referral bias, meaning that patients with normal studies will only be referred for coronary angiography when the suspicion for CAD is high. Since the majority of true negative patients will not be referred, a relatively high false positive rate will be obtained, resulting in a lower specificity. To circumvent this problem, the normalcy rate is used, which indicates the frequency of normal test results in patients with a low to intermediate likelihood of CAD. In a pooled analysis of 10 SPECT studies (n=543 patients) the normalcy rate was 89% [14].

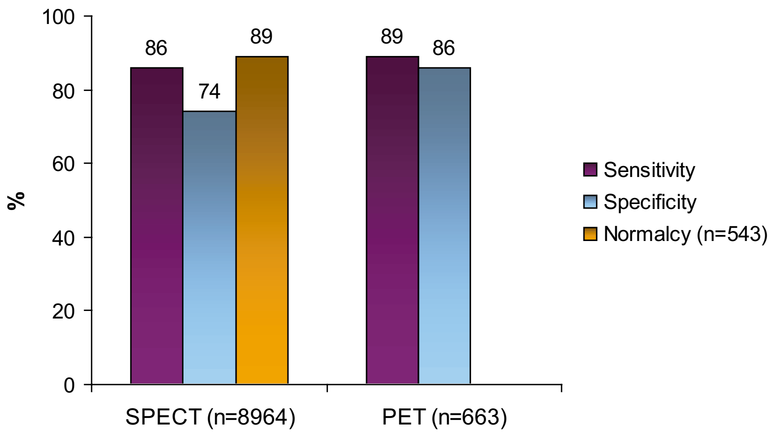

Figure 4. Diagnostic accuracy of nuclear imaging techniques to detect significant CAD (Data based on references [14;15]).

Another frequently encountered cause of reduced specificity is the occurrence of artefacts due to soft tissue attenuation that are mistaken for true perfusion defects. For this purpose, dedicated hardware and software have been developed that allow direct reconstruction of attenuation corrected images based on measurements of the attenuation distribution profile [16]. In addition, the use of ECG gated imaging, which has allowed simultaneous assessment of LV function, has led to further improvement of the diagnostic accuracy of SPECT. By identifying normal wall motion in segments with artifacts due to soft tissue attenuation, a substantial reduction in the number of false-positive test results can potentially be achieved [17]. Indeed, Smanio et al demonstrated an increase in normalcy rate from 74% to 93%, while the number of inconclusive tests decreased from 31% to 10% through addition of systolic function data to the original perfusion data [18].

Positron emission tomography. The main advantages of PET over SPECT are the systematic use of attenuation correction and the feasibility to perform absolute quantification of perfusion (ml/min/g). Nitrogen-13 ammonia, rubidium-82 and Oxygen-15 labeled water are the most commonly used tracers. Pooled analysis of 7 studies (1 study using nitrogen-13 ammonia, 4 with rubidium-82 and 2 using both) including 663 patients revealed a sensitivity and specificity of 89% and 86% to detect CAD (Figure 4) [15]. In addition to the higher specificity as compared to SPECT, another potential advantage of PET is the high spatial resolution that allows distinction between epi- and endocardial perfusion in some cases [19]. In addition, PET is the only technique that permits absolute quantification of resting and hyperemic blood flow, thereby allowing quantification of coronary flow reserve (CFR). This is of particular importance, since even in the absence of obstructive coronary artery disease, endothelial dysfunction that is associated with early atherosclerosis can be assessed by measuring CFR. Indeed, evidence is accumulating that in the presence of risk factors for CAD, including hypercholesterolemia, hypertension, diabetes mellitus and smoking, abnormal endothelial function is precedes clinically overt atherosclerotic changes in the epicardial coronary arteries [20-25]. In addition, microvascular disease can be assessed by quantitative measurements of blood flow and CFR using PET.

Thus, PET can be used to measure early atherosclerotic disease activity and resultant damage in patients with elevated risk profiles. Moreover, these measurements also permit monitoring response to different therapeutic strategies, including pharmacotherapy and life-style modification [26-28].

Echocardiography

Stress echocardiography. The hallmark of myocardial ischemia during stress echocardiography is the induction of reduced systolic wall thickening. Pooled analysis of 43 available studies on the diagnostic accuracy of exercise echocardiography (15 studies, n=1849 patients) showed a weighted mean sensitivity of 84% and specificity of 82% and 80% and 84% for dobutamine echocardiography (28 studies, n=2246 patients) (Figure 5) [29].

Contrast echocardiography. Limitations of stress echocardiography include suboptimal image quality (due to poor acoustic window or drop-out of the anterior and lateral wall) in 10-15% of patients, the operator dependency and reduced reproducibility. Second harmonic imaging as well as the use of intravenous contrast agents improve image quality. In addition, contrast echocardiography allows assessment of myocardial perfusion. The diagnostic value of stress echocardiography is enhanced by integration of perfusion and systolic wall motion abnormalities. Pooled analysis of the available studies (7 reports, n=245 patients) demonstrated a weighted mean sensitivity of 89% and a specificity of 63% (Figure 5) [30-36]. Thus, specificity of contrast echocardiography is reduced, which may

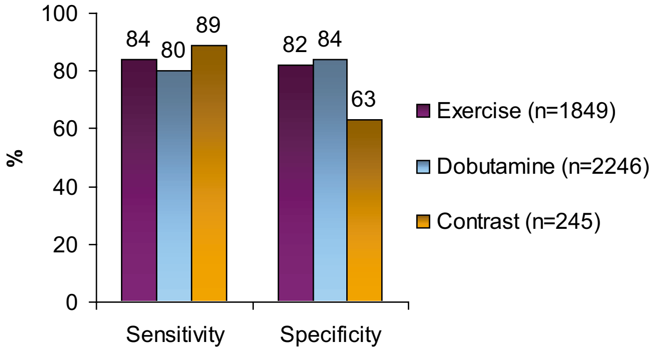

Figure 5. Diagnostic accuracy of stress-echocardiography (Data based on reference [29]).

(partially) be attributable to the still limited experience with image interpretation and optimization of data acquisition [31;32]. Furthermore, a considerable variation exists among the available studies in both acquisition protocols and stressors. Consequently, no definite conclusions on the precise diagnostic accuracy of contrast echocardiography can currently be drawn.

Magnetic resonance imaging

Myocardial perfusion is evaluated by injecting a bolus of contrast agent followed by continuous data acquisition as the contrast passes through the cardiac chambers and into the myocardium. Relative perfusion deficits are recognized as regions of low signal intensity within the myocardium. Due to the high spatial resolution of MRI, the technique is, even better than PET imaging, capable of differentiation between subendocardial and transmural perfusion defects. At present, weighted mean sensitivity and specificity, derived from 17 reports with 502 patients are 84% and 85% (Figure 6) [29;37-39].

In addition to myocardial perfusion, global and regional systolic LV function can be assessed with high accuracy with MRI as well. Pooled analysis of 10 studies (n=654 patients) yielded a weighted mean sensitivity and specificity of 89% and 84% to detect CAD (Figure 6) [29;37].

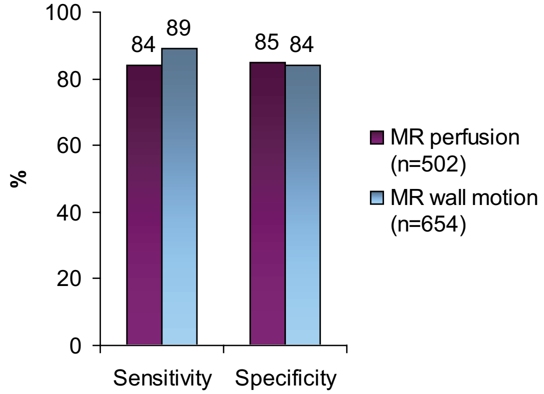

Figure 6. Diagnostic accuracy of perfusion and wall motion imaging MRI (Data are based on references [29;37-39]).

Prognosis of coronary artery disease

Besides diagnosis of CAD, non-invasive imaging also provides prognostic information. For this purpose, patients are generally classified in 3 categories. Patients are considered at low risk when the cardiac mortality rate per year is less than 1%, whereas patients are considered at high risk when cardiac mortality exceeds 3% per year. Patients with an annual mortality rate between 1% and 3% are classified at intermediate risk.
Patients with low to intermediate risk may benefit from aggressive risk factor modification, whereas invasive evaluation followed by intervention should be considered in patients with high risk.

Prognostic value of atherosclerosis

Extensive data are available on risk stratification by assessment of coronary artery calcium using EBCT. Since the presence of calcium in the coronary arteries is indicative for the presence of atherosclerosis, prognostic information can be derived from the total coronary calcium burden. However, much controversy still exists to the question whether coronary artery calcium scoring can provide prognostic information that is incremental to conventional cardiac risk assessment, as based on the Framingham model or the EuroSCORE. To address this issue, a meta-analysis of studies performing follow-up of asymptomatic individuals after EBCT calcium measurement was recently performed. Only studies that provided score-specific relative risks, adjusted for established risk factors, were included, resulting in analysis of 4 studies with a total of 3970 patients included [40]. For calcium scores in the range of 1 to 100, a summary adjusted relative risk of 2.1% was observed. Higher relative risk estimates were obtained for higher calcium scores, ranging from 3.0 to 17.0 for calcium scores higher than 400, demonstrating that coronary artery calcium score indeed provides prognostic information incremental to risk factors. These findings were further confirmed by Shaw et al, who performed a 5-year follow-up study of a large cohort of 10.377 asymptomatic individuals after coronary artery calcium scoring with EBCT [41].

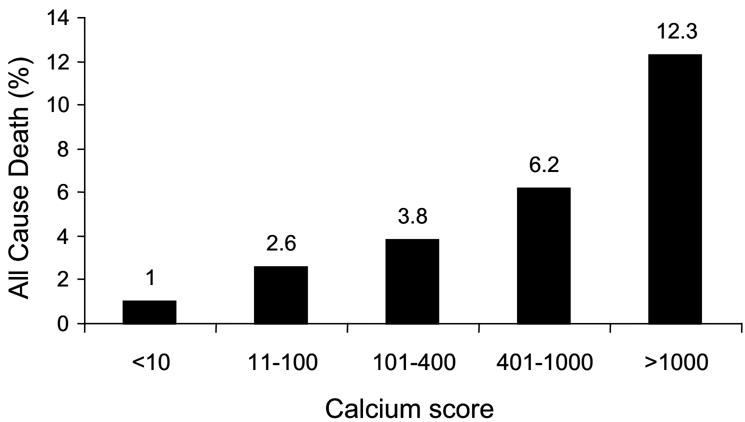

Figure 7. Prognostic value of coronary artery calcium scoring with EBCT. Data have been obtained over a 5-year follow-up period in 10.377 asymptomatic individuals with risk factors for CAD (Data based on reference [41]).

As depicted in Figure 7, patients with minimal or no calcium had an excellent survival with a mortality rate of 1%, whereas mortality increased to 12.3% for patients with a score >1000. In a risk-adjusted model of mortality, it was demonstrated that the coronary artery calcium score was indeed a strong and independent predictor of all cause mortality. In fact, the authors showed that for various Framingham risk subsets, coronary artery calcium score could provide superior prediction of death, with 5-year mortality rates increasing from 1.1% for scores <10 to 9.0% for scores >1000 in patients at an intermediate risk. Even in low-risk patients, coronary artery calcium score could provide refinement of risk stratification, with mortality rates increasing for 0.9% to 3.9% similar to above. Accordingly, coronary artery calcium screening may be used to identify those patients in whom aggressive risk reduction is needed, although the precise threshold of calcium value above which intervention is warranted is still unclear due to the wide inter-study variation.

In addition to risk stratification, measurements of coronary calcium may also be used to monitor anti-atherosclerotic effect of medical therapy. Callister et al performed both baseline and follow-up assessment after a minimum of 12 months in 149 patients without previously known CAD, referred for screening with EBCT [42]. In 105 patients lipid-lowering treatment was started at the discretion of the referring physician. In all patients, serial measurements of low-density lipoprotein (LDL) cholesterol were obtained in order to relate LDL levels to changes in calcium scores. In the untreated population, as well as in patients with LDL-levels still higher than 120 mg/dl despite medical treatment, increase in mean calcium-volume scores of respectively +52 ± 36% and +25 ± 22% (P<0.001) were observed. However, in patients that did respond to medical treatment, as reflected by LDL levels lower than 120 mg/dl, a slight decrease in calcium volumes was observed (-7 ± 23%, P=0.01). These findings suggest that EBCT calcium assessment may also allow non-invasive monitoring of response to medical therapy.

In contrast to EBCT calcium scanning, non-invasive angiography with either MRI or CT techniques is relatively new and the prognostic value of these techniques has not been established yet.

Prognostic value of ischemia

Numerous studies have ascertained the relation between the presence of stress-inducible ischemia and prognosis. Since both the induction of perfusion defects as well as wall motion abnormalities are indicative of ischemia, all techniques that assess these phenomena can theoretically be used for prognostification. Indeed, a large body of evidence has been obtained with particularly both nuclear techniques and echocardiography and risk stratification has become an integral part of these tests. Similarly, also MRI is likely to allow prognostification in addition to the diagnosis of CAD, although thus far, limited data are available.

Nuclear techniques

Single photon emission computed tomography. Of all studies dedicated to the assessment of prognosis in patients with suspected or known CAD, the vast majority have used SPECT. Recently, a meta-analysis of 31 papers comprising 69.655 patients on the prognostic value of SPECT was published [43]. A normal SPECT study was associated with an average hard event rate (cardiac death or myocardial infarction) of 0.85% per year, which is comparable to event rates in the general population without any evidence of CAD. In contrast, the hard event rate was 5.9% per year in patients with a moderately-severely abnormal SPECT study. In Figure 8, average annual event rates for normal and abnormal SPECT studies, obtained with either exercise or pharmacological stress are shown. From these data, it can be observed that studies using pharmacological stress show event rates that are slightly higher both in normal and abnormal studies, as compared to exercise testing. Accordingly, a difference in baseline characteristics and thus risk for cardiac events may exist between patients selected for pharmacological stress testing and those who can perform an exercise protocol. Moreover, exercise capacity itself has been shown to be a strong predictor of death [44] and is thus likely to influence event rates observed after stress testing. This observation was recently confirmed by Navare and colleagues [45] who performed a meta-analysis of 24 studies evaluating prognosis with either pharmacological or exercise stress SPECT comprising 14.918 patients. Although based on the similarity of the obtained odds ratios and ROC curves risk stratification was shown to be comparable between both techniques, high event rates were observed with pharmacological stress. Indeed, comparison of demographics revealed that patients selected for this type of stress were in general older, and had a higher prevalence of other factors of poor prognosis, including type 2 diabetes mellitus or previous myocardial infarction.

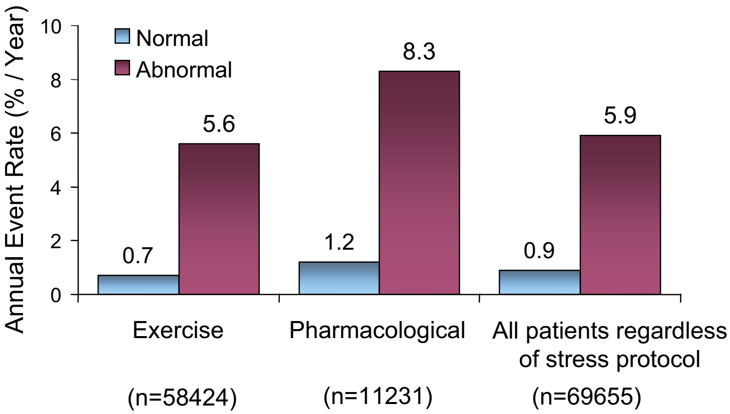

Figure 8. Prognostic value of SPECT, obtained in 69655 patients. Numbers between parentheses are number of patients included (Data are based on reference [43]).

Accordingly, these findings underline the relevance of the type of stress used as well as the individual patient's characteristics when interpreting the prognostic significance of a functional imaging study.

It is well known that LV function (LV ejection fraction) and LV volumes also provide powerful prognostic information [46;47]. With the introduction of gated SPECT, it became possible to integrate information on perfusion and function. Sharir et al were the first to demonstrate the strong prognostic power of gated SPECT when perfusion and function data were integrated in 2.686 patients with a mean follow-up of 21 ± 4.6 months [47]. After adjustment for clinical information, the amount of perfusion defect reversibility was demonstrated to be the strongest predictor for non-fatal myocardial infarction, whereas cardiac death was best predicted by post-stress left ventricular ejection fraction. This observation is of interest and supports the idea that ischemic events (e.g. infarction) are best predicted by the extent of reversible perfusion abnormalities, whereas the extent of scar tissue as reflected in the severity of reduction in LVEF is most predictive of cardiac death. Recent data suggest that further refinement of risk stratification can be achieved using end-diastolic and end-systolic volume measures in addition to LVEF [48]. Also, the observation of transient ischemic dilatation during stress has been shown to be associated with worse prognosis, even in the presence of normal myocardial perfusion [49]. Particularly in such settings, when perfusion is normal or near-normal, these ancillary findings can have important implications for prognosis that would have been deemed to be excellent on the basis of the perfusion data only.

Accordingly, functional imaging with SPECT has become an established modality in the identification of patients at elevated risk and who may benefit from more aggressive medical therapy or revascularization.

Positron emission tomography. Currently, minimal data are available on the prognostic value of PET. Marwick et al evaluated the prognostic value of rubidium-82 PET in 685 patients with suspected or known CAD after a mean follow-up of 41 months [50]. Mortality rate was significantly less in patients with a normal PET study (0.9%) as compared to patients with an abnormal study (4.3%). When all events, including also myocardial infarction, unstable angina and late (>3 months after the initial PET study) revascularization, were taken into account, a normal examination was associated with a 90% event-free survival, whereas event-free survival in patients with small, moderate and extensive abnormalities were 87%, 75% and 76% respectively. Based on Cox proportional-hazards models, the PET results were demonstrated to be incremental to those of clinical and angiographic evaluation. Accordingly, PET may be a valuable alternative for prognostification, particularly in patients that are technically challenging to image with SPECT, such as obese patients or with extensive previous infarction.

Echocardiography

Besides SPECT, stress echocardiography is often used for risk stratification in patients with suspected or known CAD. Similar to SPECT, it has been shown that a negative stress echocardiogram is associated with an excellent prognosis allowing identification of patients at low risk [51]. Pooled analysis of 13 stress echocardiography studies with 32.739 patients included, revealed an annual hard event rate (death or myocardial infarction) of 1.2% for a normal stress echocardiogram as compared to 7.0% for an abnormal study [52-64]. In Figure 9, annual event rates for normal and abnormal studies are depicted for stress echocardiography according to the different stressors used. Although the emerging use of simultaneous assessment of myocardial perfusion by means of contrast administration is likely to enhance the prognostic value of stress echocardiography, no data are currently available to support this notion.

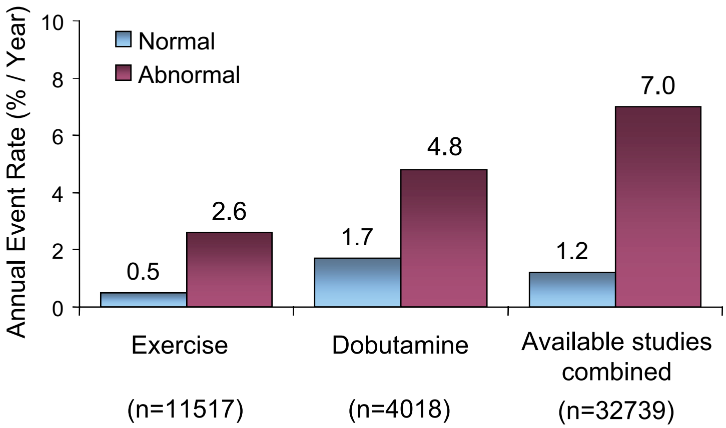

Figure 9. Annual event rates (death or myocardial infarction) of normal and abnormal stress echocardiograms, obtained by pooled analysis of 13 studies with 32739 patients. Numbers between parentheses are number of patients included. For the individual analyses of either exercise or dobutamine stress only studies specifically stating the use of either exercise or dobutamine stress were included, while studies performing different stress protocols interchangeably during the study protocol were disregarded. However, these studies were included in the combined analysis of all available studies. (Data based on references [52-64]).

Magnetic resonance imaging

Currently, only limited data on the value of MRI for prognosis in CAD are available. No prognostic data on MRI perfusion assessment are available, and only one study has evaluated the prognostic value of MRI wall motion assessment for prognostification. Hundley and colleagues performed stress-rest MRI and focused on systolic wall motion. The study comprised 279 patients who were referred for MRI because of poor LV endocardial border delineation on echocardiography [65]. Patients were categorized according to the presence, extent, and location of inducible wall motion abnormalities during dobutamine/atropine administration and according to the LVEF being <40% or ≥40%. Over a mean follow-up period of 20 months, the annual hard event rate, defined as the occurrence of cardiac death or myocardial infarction, was 2% in the patients preserved LVEF (≥40%) without ischemia. Conversely, the annual hard event rate was 13% in the patients with depressed LVEF (<40%), regardless of the presence of ischemia. In patients with a LVEF ≥40% and evidence of inducible ischemia the annual hard event rate was 10.6%. These data illustrate the potential role of MRI for prognosis in patients with suspected or known CAD, but larger studies are needed.

Summary and Future Perspectives

With the increasing number of patients referred for evaluation of the presence and extent of CAD, non-invasive imaging techniques have become very important in the clinical patient management. Initially, the available techniques relied on visualization of ischemia using myocardial perfusion (with nuclear imaging techniques) or systolic wall motion (with echocardiography). With recent technical developments, both nuclear imaging and echocardiography currently allow assessment of both perfusion and systolic function, thereby enhancing their diagnostic accuracy. Similarly, MRI can also provide integrated assessment of perfusion and systolic wall motion, with a comparable accuracy to SPECT and echocardiography. In addition to the diagnosis of CAD, SPECT and echocardiography have been used extensively for risk stratification.

Besides the evaluation of ischemia with the established non-invasive imaging techniques, the assessment of coronary artery calcium with CT techniques, and even non-invasive angiography with MSCT and MRI is shifting the emphasis from ischemia detection to assessment of preclinical atherosclerosis and coronary anatomy. Although these techniques appear very accurate for exclusion of atherosclerosis, it is currently unclear what the clinical value is when these examinations demonstrate atherosclerosis. The following case report is presented to illustrate this dilemma.

A 54-year old man presented to the outpatient clinic with atypical chest pain, smoking and hypercholesterolemia. The patient was referred for further evaluation using gated SPECT and non-invasive angiography using MSCT. The SPECT study was performed using bicycle exercise; blood pressure and heart rate response were normal, exercise capacity was adequate, the exercise ECG

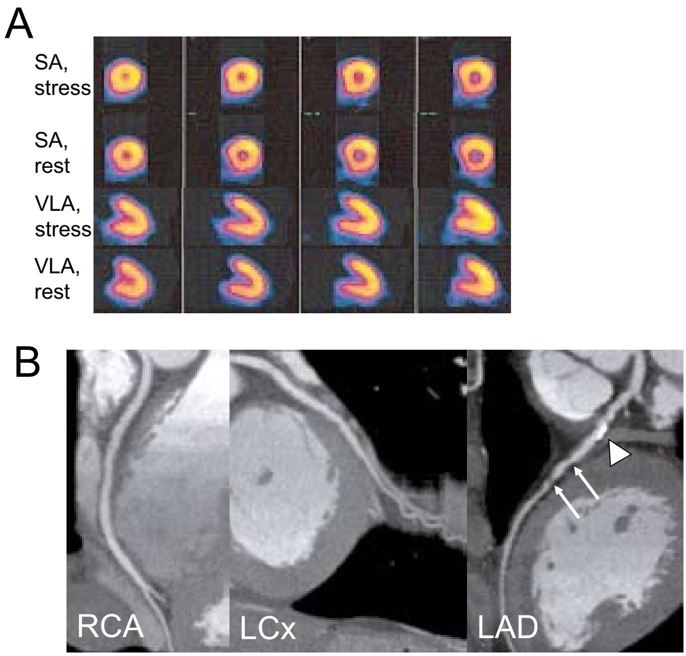

Figure 10. Non-invasive imaging in a 54-year old man with suspected CAD. SPECT perfusion imaging demonstrated normal myocardial perfusion in all territories (Panel A). MSCT coronary angiography was also performed (Panel B). From the left to the right, curved multiplanar reconstructions are shown of the right coronary artery (RCA), left circumflex (LCx) and left anterior descending coronary artery (LAD). Only minor wall irregularities were observed in the RCA and LCx. In the LAD however, a proximal extensive calcified lesion (arrow head) and various non-calcified plaques (arrows) were observed.

Abbreviations: LAD: left anterior descending coronary artery, LCx: left circumflex coronary artery, RCA: right coronary artery, SA: short-axis, VLA: vertical long-axis.

did not show ischemia and angina was not reported. The LVEF on the gated images was 63%, LV volumes were normal. No perfusion abnormalities were observed during SPECT imaging, as shown in Figure 10A. In Figure 10B, the results of the MSCT study are shown. Only minor wall irregularities were observed in the right and left circumflex coronary artery. The left anterior descending coronary artery however, showed a significant calcified lesion and various non-calcified plaques in the proximal and mid part of the vessel.

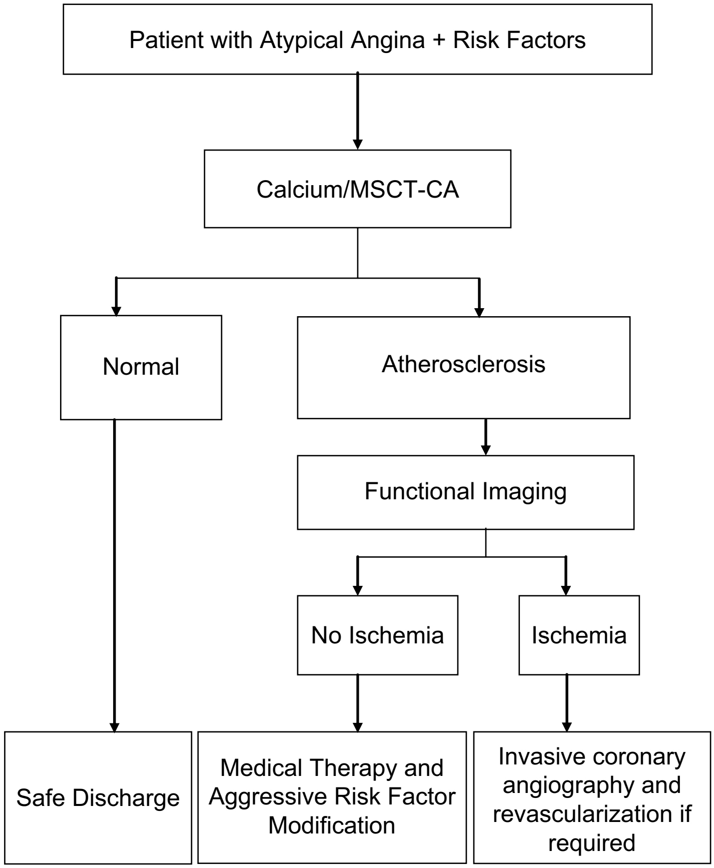

Figure 11. Flow-chart for patients presenting with an intermediate likelihood of CAD in which MSCT (calcium scoring and coronary angiography) is used as a first-line evaluation tool. Patients with normal coronary arteries can be discharged safely. If atherosclerosis is observed however, patients are referred for functional imaging to determine the presence of ischemia. Consequently, patients with inducible ischemia are then referred for invasive coronary angiography, potentially followed by revascularization. If no ischemia is demonstrated, patients can be managed with medical therapy and aggressive life-style and risk factor modification.

These findings now raise the question how this patient should be further treated. Should coronary angiography be performed (with potential intervention) based on the lesions visualized on MSCT or should aggressive medical therapy and risk factor modification be proposed based on the absence of ischemia on the SPECT study?

Accordingly, algorithms are needed on when to use which of the 2 main categories of non-invasive imaging: ischemia detection and atherosclerosis imaging. A potential algorithm is proposed in Figure 11. First, imaging should mainly be applied to patients with an intermediate likelihood of CAD. In these patients, who present with either atypical angina or who are even asymptomatic but have an elevated risk profile due to the presence of coronary risk factors (e.g. type 2 diabetes mellitus), a first step could be to assess coronary artery calcium or non-invasive angiography. In the absence of coronary atherosclerosis, further imaging may not be needed and the patient can be reassured. In the presence of atherosclerosis, assessment of ischemia is needed. When ischemia is absent, risk factor modification and aggressive medical therapy is indicated. When ischemia is present, invasive evaluation (and potential intervention) should follow. The required information can be gathered by sequential testing using CT technology (to assess atherosclerosis/anatomy) and a technique that allows assessment of ischemia (i.e. SPECT, PET, echo or MRI), or integrated imaging, which is possible with PET-CT (or maybe in the near future with SPECT-CT).

Indeed, hybrid or dual-modality imaging offers the promising prospect of co-registration of anatomic landmarks with physiological data. Since the CT images can be used for attenuation correction, both efficiency and image quality of PET data acquisition is likely to improve, thereby enhancing its diagnostic accuracy while reducing data acquisition time substantially. On the other hand, incremental information will be added to the MSCT examination, since PET will provide data on the pathophysiological impact of the detected lesions, which is needed to determine treatment strategy. Accordingly, the simultaneous assessment of coronary lesions and their pathophysiological impact is likely to enhance diagnostic certainty and optimize clinical decision-making, as recently demonstrated by Namdar et al [66]. From a practical point of view however, incorporation of CT with SPECT systems may be preferable in daily clinical routine, and fusion of these two modalities is currently under development.

In conclusion, non-invasive imaging is a powerful tool in the diagnostic and prognostic work-up of patients with suspected or known CAD. Integration and fusion of imaging technologies will be the future in management of patients, with a focus on integration of information on atherosclerosis and ischemia.

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