Multimodality imaging in chronic coronary artery disease

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Chapter 1

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

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Abstract

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 (SPECT), positron emission tomography (PET), (contrast) stress echocardiography and cardiac magnetic resonance (CMR) and these techniques can be characterized as functional imaging techniques as they detect ischemia. Although the presence of a flow-limiting stenosis can be adequately ruled out with these techniques, atherosclerosis can not be visualized with functional techniques. For this purpose, non-invasive coronary angiography techniques (computed tomography, 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 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. Firstly, 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 imaging (CMR). 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 can not be demonstrated. Nonetheless, as increasingly interest is directed towards early detection in particular, knowledge of pre-clinical 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 of evaluation of coronary calcium burden or non-invasive coronary angiography with multi-slice 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

Multi-slice computed tomography

Calcium score

Computed tomography (CT) has been available for cardiac imaging since the early nineties. The first investigations were performed with electron beam computed tomography (EBCT), predominantly for the assessment of coronary calcium scores. With EBCT, x rays are created through an electron beam that is guided by a 210º 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 which allow simultaneous acquisition of a number of slices with a certain overlap. While 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 compared with MSCT. Quantification of calcium in the coronary arteries can be realized with the Agatston score.[1] In general, a score of 1 to 10 is considered minimal, 11 to 100 mild, 101 to 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 five-year risk-adjusted survival for patients with a calcium score of ≤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.

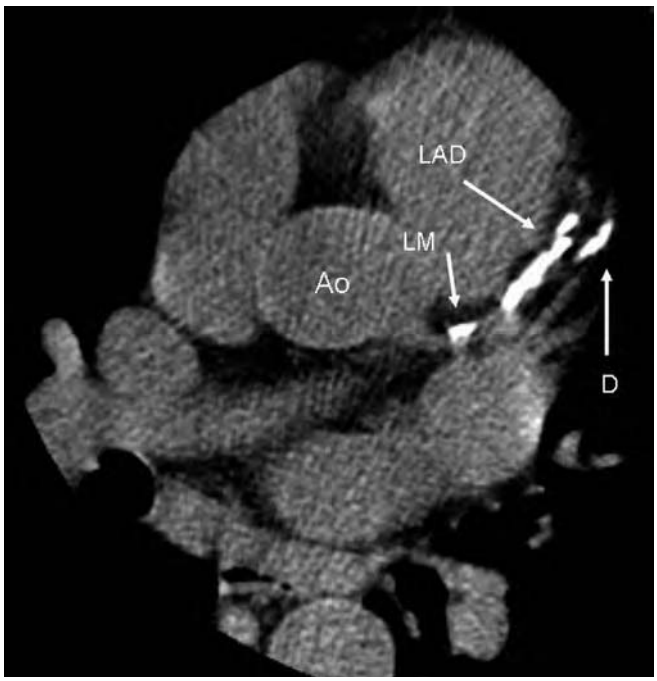

Figure 1. Example of a patient with a high calcium score. Ao: Aorta. D: Diagonal branch of the left anterior descending coronary artery. LM: Left main coronary artery. LAD: Left anterior descending coronary artery. Calcifications appear as bright white dense structures on the MSCT images.

Coronary angiography

With the introduction of the MSCT, the first step towards non-invasive evaluation of the coronary arteries with computed tomography techniques was made. Although the initial results with the 4-slice MSCT were promising, 20% of the coronary segments had to be excluded from evaluation due to non-diagnostic quality.[4] The introduction of the 16-slice and at present the 64-slice MSCT has led to substantial improvement in resolution due to submillimeter 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).[5] Invasive coronary angiography was used as the gold standard for assessment of significant coronary artery stenosis (defined as >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 detection of significant coronary stenosis, while the overall specificity was even higher, 94%. Similar percentages were observed in the analysis of stented lesions. Eight percent of all segments were of non-diagnostic quality. A meta-analysis based on 1778 patients[4 6-13] (**Figure 2**) shows that the weighted mean sensitivity and mean specificity for detection of significant CAD have increased to 91% and 96% respectively with the 64-slice MSCT scanner.

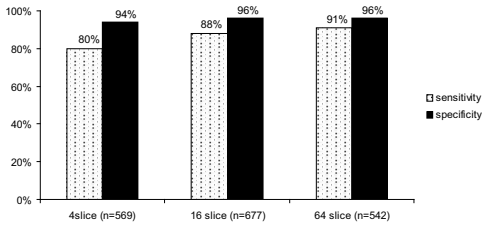

Figure 2. Diagnostic accuracy of 4-slice, 16-slice and 64-slice MSCT for the detection of significant coronary artery disease.

Nevertheless, certain short-comings 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 artifacts 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 as compared to conventional coronary angiography is the ability to image the atherosclerotic lesions directly and it may allow distinction between different plaque types. Indeed, Schroeder et al.[14] demonstrated significantly different mean densities of 419±194 HU, 91±21 HU and 14±26 HU for respectively calcified, mixed and soft plaques (as classified by 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, while also further distinction of low-density plaques in fibrous and lipid content appears at least in the near future not feasible 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 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 can be evaluated as well as regional wall motion. Belge and colleagues[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.[16] with correlation coefficient of r=0.97 for all above mentioned parameters. However, due to the relatively high radiation dose, MSCT imaging for evaluation of cardiac function alone is currently not preferable.

The duration of a MSCT angiography examination ranges from 10 to 15 minutes, depending on the imaging protocol used. The actual scan time has been reduced to approximately 10 seconds with the introduction of the 64-slice MSCT. Accordingly, the majority of procedural time is used for patient preparation and determining of scanning positions.

Cardiac magnetic resonance 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 resolution 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.[17] have investigated the accuracy of coronary angiography with CMR in 109 patients with suspected CAD in a prospective, multicenter study. In each patient, 7 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.[17] 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 compared with free breathing alone.[18] 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% with a specificity of 87%.[4] Nevertheless, diagnostic accuracy as well as the percentage interpretable segments is still not sufficient for routine clinical application while 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 to 60 minutes, 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 due to 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.[19] 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.[20 21] Saam et al.[22] 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.[22] 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 ischemia

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 ischemic cascade[23], perfusion abnormalities are induced at an early stage, followed by diastolic and systolic LV dysfunction (**Figure 3**). Suitable imaging modalities for this purpose are gated single-photon emission computed tomography (SPECT), positron emission tomography (PET), stress echocardiography (with contrast) and CMR.

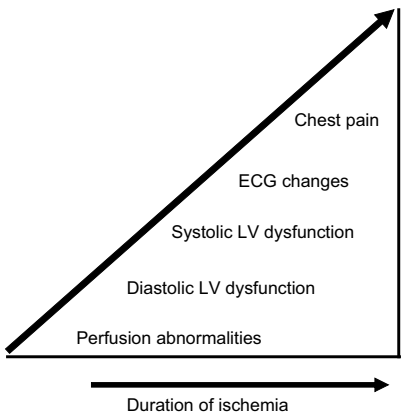

Figure 3. The ischemic cascade reflecting the order in which pathophysiological changes during ischemia will occur.

Nuclear imaging

Single photon emission computed tomography

Evaluation of myocardial perfusion with stress and rest myocardial perfusion SPECT has become a corner stone in the management of patients with known or suspected CAD.[24] 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 as compared to imaging modalities that rely on the induction of wall motion abnormalities.

Myocardial perfusion

For the evaluation of myocardial perfusion, 2 datasets are commonly acquired: one at rest and one after (physical or pharmacological) stress. The presence of reversible (indicating ischemia) 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 tracers are available for assessment of myocardial perfusion: thallium-201, technetium-99m sestamibi and technetium-99m tetrofosmin. The technetium-99m labeled 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, since perfusion abnormalities occur early in the ischemic 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%.

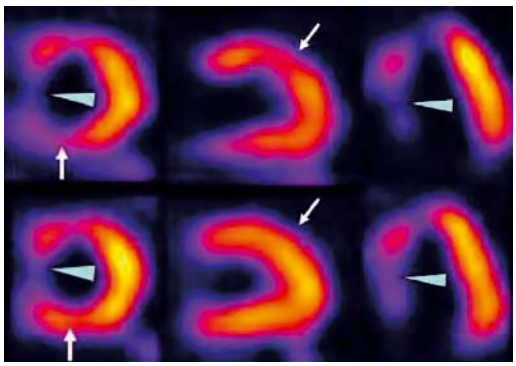

Figure 4. Example of a patient with a reversible defect as well as an irreversible defect on perfusion SPECT. Example of a patient with reversible perfusion defect in the inferior (white arrows short axis images) and anterior wall (white arrows vertical long axis images), and an irreversible perfusion 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, the lower panel shows the same reconstructions during rest.

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 less than 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 ejection fraction as well as evaluation of regional wall motion has become routine practice. Meta-analysis of 9 studies (n=164 patients) revealed excellent correlations between gated SPECT and CMR for the evaluation of LV volumes and ejection fraction.[27] In addition, an excellent agreement of 83% between gated SPECT and CMR for 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 artifacts. 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 approximately 18 to 23 minutes, depending on the imaging protocol used. The complete investigation including patient preparation will take approximately 90 minutes per dataset. 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 (milliliters per gram per minute), which may be important in patients with homogeneous reduced perfusion (e.g. patients with heart transplants or patients with balanced ischemia 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, 3 different tracers can be used: 2 tracers that are extracted (rubidium-82 and nitrogen-13 ammonia) and 1 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 minutes 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 7 PET studies (1 study using N-13 ammonia, 4 using Rb-82 and 2 using both) including 663 patients thus far showed high sensitivity of 89% and a specificity of 86% for the detection of CAD.[29]

An important advantage of PET is the quantification of coronary flow reserve (CFR) 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. with diabetes mellitus or hypercholesterolemia) but yet without clear significant coronary stenoses[31 32], thereby providing an opportunity for monitoring of response to therapy and life-style 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 will take approximately 100 to 120 minutes (rest and stress imaging together), while a complete examination with rubidium-82 will take approximately 44 minutes (rest and stress imaging).[33] Similar to 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 ischemia, while wall motion abnormalities in rest in general represent infarcted myocardium.[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%.[35] 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%.[35] Comparison of exercise stress with dipyridamole stress by means of meta-analysis of 8 studies (n=533 patients) demonstrated a significantly higher sensitivity for detection of inducible myocardial ischemia for the former (79% vs. 72%, $P < 0.05$).[36] Specificity on the other hand, was higher for dipyridamole stress echocardiography (92% vs. 82%, $P < 0.05$). As a result, diagnostic accuracy of both tests appeared to be comparable (77% for dipyridamole vs. 80% for exercise stress echocardiography, P=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 micro bubbles will reside in the vascular space until they dissolve, and can therefore be used for evaluation of the micro vascular circulation. Recently, a large multicenter 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.[37] This study, in 123 patients, demonstrated that the accuracy of MCE is comparable to that of SPECT, both on patient level as well as 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.[38] Integration of systolic wall motion abnormalities and perfusion may further enhance the diagnostic value of the test. The duration of a standard echocardiographic examination is approximately 20 to 30 minutes.

Cardiac magnetic resonance imaging

Cardiac function

In patients with ischemic 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 coronary artery disease.[39] Owing to its excellent resolution, CMR has been established as a precise and highly reproducible modality for measurement of LV systolic and diastolic function.[40] In addition, regional wall motion assessed with CMR can be accurately evaluated, which may provide information on myocardial viability. Accordingly, CMR is currently considered to be the gold standard for the assessment of cardiac function.[41] 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 detection of ischemia, with a mean weighted sensitivity of 89% and a mean weighted specificity of 84%.[35 42]

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, ischemic 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%.[35 42-44] Another commonly used technique is delayed contrast enhancement with CMR, which provides information on the extent of scar tissue. Ten to 15 minutes post injection of gadolinium-DTPA, the contrast will have disappeared in normal myocardium, whereas scar tissue will appear as a hyperenhanced area on the CMR images (**Figure 5**). As the technique has a high spatial resolution, distinction between subendocardial and transmural infarctions is possible in contrast to other modalities.[45]

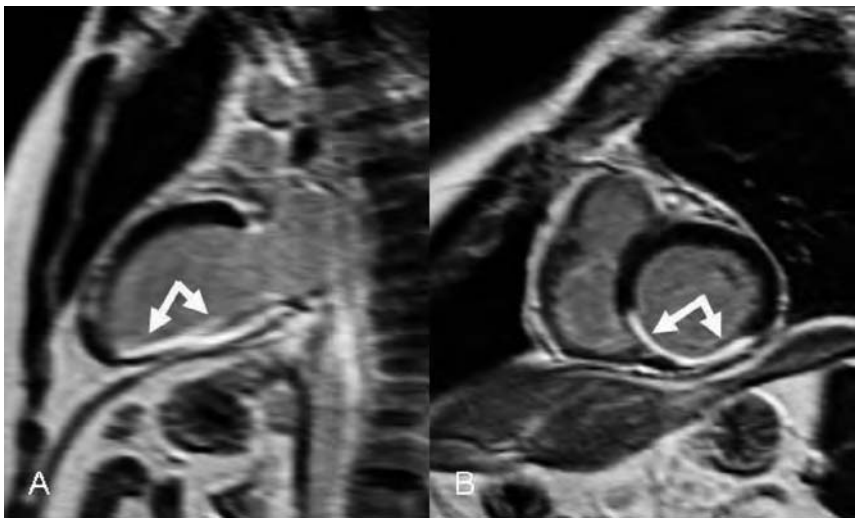

Figure 5. Example of a patient with delayed contrast enhancement on CMR. Panel A: Vertical long axis image with delayed enhancement (white arrows) in patient with prior inferoposterolateral infarction. Panel B: Short axis image with delayed enhancement (white arrows) of the same patient.

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 ischemia served as gatekeeper for invasive coronary angiography. More recently, the emphasis has 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 that may benefit from further testing as well as treatment. However, based on the anatomical studies, one can not determine the presence and extent of ischemia, 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. On the other hand, if atherosclerosis is demonstrated, additional evaluation is warranted to assess the presence of myocardial ischemia (by means of gated SPECT, PET, stress and/or contrast echocardiography, or CMR). If ischemia is detected, invasive angiography and possibly even intervention is indicated. In contrast, medical therapy and aggressive risk profile modification may be the preferred therapeutic regimen in case of absence of ischemia.

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 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 ischemia. 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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