Chapter 1

General introduction and outline of the thesis

Published in part as:
Towards a non-invasive anatomical and functional diagnostic work-up of patients with suspected coronary artery disease.

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Netherlands Heart Journal 2010 May;18(5):270-3.

Coronary artery disease and myocardial ischemia

In the Netherlands, coronary artery disease (CAD) is the second most important cause of death for men and the third for women. A total of 10.832 persons died of CAD in the Netherlands in 2010. Furthermore, according to a national survey in 2009, 3.2 % of all men and 1,5% of all women in the Netherlands have a history of myocardial infarction. Additionally, CAD was the cause of 86.815 hospital admissions in 2007. (1) Chest pain may be the first symptom of patients with CAD. In the presence of a stenosis in a coronary artery, an increased oxygen demand of the myocardium e.g. during exercise, may lead to a mismatch between oxygen supply and demand. Consequently, a complex group of pathophysiologic changes is initiated that is called the ischemic cascade, see figure 1. (2) As a result of this mismatch between oxygen supply and demand, relative myocardial perfusion is reduced and subsequently, diastolic and systolic dysfunction decline. If this mismatch persists, electrophysiologic changes can be detected by electrocardiography and ultimately the patient may feel chest pain. When the patient rests, oxygen demand decreases and the mismatch disappears. Subsequently, chest pain, diastolic and systolic function and relative myocardial perfusion will resolve.

Diagnostic evaluation of suspected coronary artery disease

To decide which diagnostic test is most appropriate for a patient with suspected CAD, the pre-test probability of having CAD is calculated for each patient presenting with chest pain. According to the Bayesian theory, the diagnostic value of diagnostic tests depends on the pre-test probability of the patient (population) that is investigated. Therefore, the pre-test probability is important for the decision which test the patient should undergo. Several risk scores have been developed using many different parameters. The most important variables that are used in clinical practice are type of chest pain, gender and age. Chest pain can be categorized in three types. Typical chest pain: 1) substernal chest discomfort with a characteristic quality and duration that is 2) provoked by exertion or emotional stress and 3) relieved by rest or NTG. Atypical angina, meeting 2, and non-anginal chest pain, meeting one or none of the characteristics. (3) From these variables, a pre-test probability of having CAD can be estimated, which is categorized as low, intermediate or high. According to clinical guidelines, patients with severe symptoms with a high pre-test probability of CAD can be referred for invasive coronary angiography. (3) As invasive testing involves substantial costs and can have serious complications, patients with an intermediate or low pre-test probability of having CAD are referred for non-invasive diagnostic tests. When these non-invasive tests show findings consistent with significant myocardial ischemia, patients can be referred for invasive coronary angiography.

Until the development of cardiac CT, all non-invasive diagnostic modalities were based on the detection of any of the pathophysiologic changes that develop during myocardial ischemia (function), rather than visualization of the atherosclerotic plaque (anatomy), see figure 1. Based on the order of these changes, assessment of myocardial perfusion seems the most promising way of early detection of ischemia.

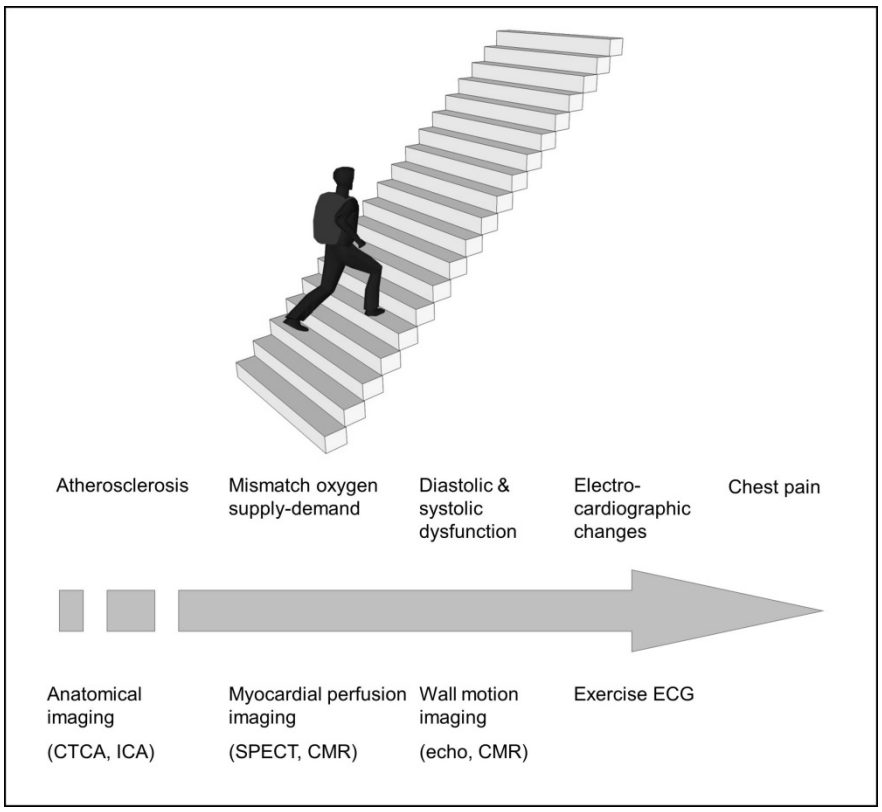

Figure 1. Association of ischemic cascade and diagnostic modalities.

Although the diagnostic evaluation of patients with suspected coronary artery disease (CAD) is part of the daily routine of cardiology practice, the conventional modalities for detection of CAD have major limitations. Even though its prognostic value has been validated extensively, exercise electrocardiography (X-ECG) has only limited diagnostic value for detection of significant CAD, with a reported average sensitivity and specificity of 68% and 77%, respectively.(4) Additionally, in a large proportion of patients results are inconclusive e.g. due to pre-existent electrocardiographic abnormalities, motion artifacts interfering with reliable ST-segment interpretation or the inability of the patient to reach the desired level of exercise because of non-ischemic limitations. Although single photon emission computed tomography myocardial perfusion imaging (SPECT) is more sensitive for detection of significant CAD, it has only a moderate specificity.(5) Consequently, this leads to a considerable number of unnecessary referrals for invasive coronary angiography. Furthermore, a combined SPECT stress and rest protocol imposes a significant radiation burden (10-20 mSv), and requires 2 separate scanning sessions. Although several studies have shown good diagnostic accuracy of dobutamine stress echocardiography (DSE) for detection of significant CAD (6-8), its routine use in daily cardiology practice is limited by

a number of factors. Most importantly, visual assessment of stress related regional wall motion abnormalities is challenging and requires a considerable amount of expertise. Even with the latest systems and techniques, suboptimal echocardiographic windows are not a rare finding and may require the use of contrast agents to improve visualization of the left ventricular endocardial border. Furthermore, DSE is a relatively time-consuming examination for the busy echocardiographic department and the use of high dose dobutamine stress bears a (small) risk (9) of ventricular arrhythmias.
In clinical practice, there is excess use of diagnostic modalities and a large number of unnecessary, false positive referrals for ICA. A recent study by Patel et al. (10) in 398,978 patients showed that only 37.6% of patients that are referred for invasive coronary angiography indeed had significant CAD. Thus, 62.4 % of patients were falsely referred for ICA. Therefore, the (non-invasive) diagnostic work-up of patients with suspected CAD needs further improvement.

Cardiac computed tomography

Recently cardiac computed tomography (CT) has been developed and is increasingly used in clinical practice. In contrast to all other non-invasive diagnostic modalities, it does not visualize myocardial ischemia, but can accurately detect coronary atherosclerosis. With the development of multidetector CT and improvement of gantry rotation times sufficiently high spatial and temporal resolutions were accomplished that made visualization of the coronary anatomy by CT possible. In multidetector CT scanners several detector rows are placed side to side and thus in one single rotation a larger part of the body (heart) is covered. During the last decade CT has evolved from 16- slice to 64- and 320-slice CT scanners, that can cover the heart (16 cm) in one rotation. Further technical developments have made low gantry rotation times possible and with the development of dual source CT scanners temporal resolution has improved even more. As a result, both total scan time and radiation dose has been reduced considerably. Although temporal resolution has improved, a stable and low heart rate are still very important for sufficient image quality. Therefore, in clinical practice, most patients receive beta-blocker (orally and/or intravenously) before start of the scan. After positioning the patient on the scan table, a non-contrast scan is acquired for calcium scoring. Then the automatic bolus tracking is planned by drawing a region of interest in the ascending aorta on a single axial slice located at the bifurcation of the pulmonary trunk. The CTCA scan can then be started automatically when the contrast level in the region of interest reaches a threshold value after injection of a non-ionic contrast agent. Overall, a cardiac CT examination, including patient preparation, takes around 15 minutes. After image acquisition, axial datasets are reconstructed at a specific phase of the RR interval, but additional datasets can be reconstructed at different RR intervals if needed. Dedicated software programs are used to analyse these axial datasets in combination with additional curved multiplanar reconstructions of the coronary arteries when needed. Furthermore, quantitative analysis can be performed using automated

quantitative analysis software (QCA), however, this has not yet replaced qualitative analysis in clinical practice.
In recent years, cardiac CT evolved from a technique that only provided information about calcified plaque burden (coronary calcium score) to a technique that can accurately visualize coronary anatomy and its atherosclerotic plaque.
In contrast to conventional functional techniques, CTCA detects CAD at a much earlier stage, when it may not have yet become hemodynamically relevant. Since acute myocardial infarctions may result from rupture of only mildly stenotic atherosclerotic plaques, detection of these plaques has significant prognostic relevance.(11) Several studies have investigated the diagnostic performance of CTCA for the detection of significant CAD.(12) In the majority of studies the negative predictive value of CTCA for detection of CAD was excellent. Therefore, this technique is particularly valuable for ruling out CAD in patients at low risk of having CAD.(13) Accordingly, recent guidelines included CTCA for patients with low or intermediate probability CAD.(14, 15) However, most studies were performed in patients with intermediate to high pre-test probability of having significant CAD and were already scheduled for ICA. Although its negative predictive value is high, the positive predictive value is quite low due to beam hardening artifacts of calcified atherosclerotic plaques, causing overestimation of stenosis severity. Furthermore, several studies have shown that CTCA cannot accurately predict the hemodynamic relevance of CAD.(16, 17) Thus, when severe CAD is detected by CTCA, additional non-invasive functional testing may be needed to assess the hemodynamic significance of disease, before referral for invasive coronary angiography.

Cardiovascular magnetic resonance imaging

Cardiovascular magnetic resonance (CMR) imaging has evolved from an effective research tool into a clinically established imaging modality for the evaluation of ischemic heart disease. (18) CMR provides anatomic and functional information in acquired and congenital heart disease and is considered the gold standard for quantification of ventricular volumes, function and mass. Late gadolinium enhanced CMR is an accurate and robust method to depict and quantify regional myocardial scarring, and can be used in the diagnosis and management of heart disease of ischemic as well as non-ischemic origin. (19,20) Adenosine stress and rest first pass magnetic resonance myocardial perfusion imaging can accurately detect myocardial ischemia. It has been validated against positron emission tomography (21), fractional flow reserve (22) and intracoronary flow measurements.(23) Recently, it has been shown that CMR myocardial perfusion imaging has at least a similar diagnostic performance for detection of significant CAD as SPECT.(24, 25) Furthermore, several studies have shown a similar prognostic value of CMR in comparison to SPECT.(26, 27)
In first pass magnetic resonance myocardial perfusion imaging an extra-cellular contrast agent is used as a flow tracer through the myocardium during pharmacological stress

(hyperemia during adenosine infusion) and at rest. The contrast agent is intravenously injected and diffuses within the interstitial space (first pass). Myocardial signal intensity increases along with the first passage of the contrast agent through the myocardium, and a perfusion defect caused by a significant coronary artery stenosis can be seen as a region of relative lower signal intensity. During contrast injection, every heart beat 3 short axis slice images (basal, mid, apex) are acquired. As this requires a high temporal resolution, a fast gradient echo sequence is used along with parallel imaging techniques. To limit motion artifacts, the first pass images are acquired during breath hold. An example of a first pass protocol is presented in figure 2.

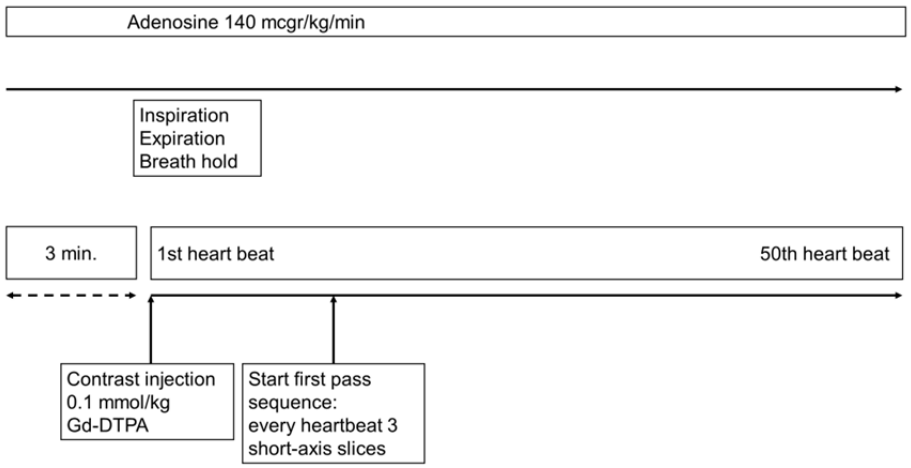

Figure 2. Adenosine first pass perfusion magnetic resonance myocardial perfusion imaging protocol.

Ten minutes after the stress scan, the rest scan is started, using identical scan parameters and contrast injection protocol, but without adenosine infusion. During the stress and rest scan, a total of 0.2mmol/kg bodyweight of contrast is injected and therefore late gadolinium enhancement images can be acquired without the use of extra contrast agent. A typical CMR ischemia protocol consists of assessment of left ventricular function, stress and rest perfusion and also includes late gadolinium enhancement imaging for the detection of irreversible scar tissue, see figure 3.

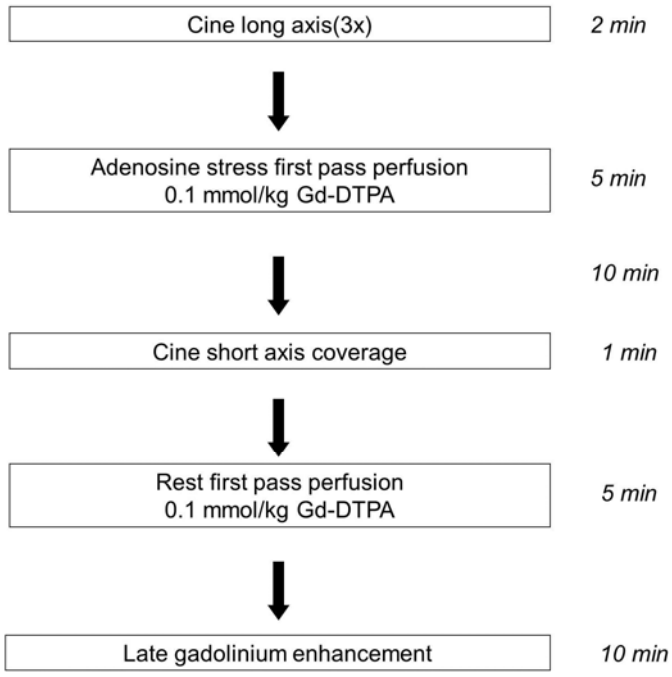

Figure 3. Typical CMR ischemia imaging protocol

First pass myocardial perfusion images can be analyzed qualitatively, semi-quantitatively and fully quantitatively. For clinical purposes, visual, qualitative analysis is generally done during or directly after the examination. In semi-quantitative analysis, signal intensity versus time curves per segment are used. Although less observer dependent, semi-quantitative analysis is more time consuming because it requires manual tracing of subendocardial and subepicardial contours. In fully quantitative analysis, absolute myocardial perfusion (ml/mm^3 tissue) can be calculated using the mathematical process of Fermi model-constrained deconvolution. (28) Although this technique seems promising, standardized acquisition and analysis protocols are still in development. Several different contrast dose protocols are being investigated to correct for the non-linear relation between signal intensity and contrast concentration.

Combined functional and anatomical assessment

The combined use of CTCA and myocardial perfusion imaging allows the non-invasive assessment of both coronary anatomy and function. Recently several studies have investigated the combined use of CTCA with nuclear perfusion imaging modalities (SPECT or PET). (17, 29-33). It was shown that the combination of both techniques may improve diagnostic accuracy for the detection of hemodynamically relevant CAD and improve risk stratification.

CMR myocardial perfusion imaging has several advantages in comparison to nuclear perfusion imaging modalities: it can provide information about the presence of myocardial ischemia, ventricular function and assessment of myocardial viability in one single scan session and it does not involve any ionizing radiation. Therefore, CMR may be the ideal additional functional imaging technique to CTCA in the diagnostic work-up of patients with suspected CAD. A typical case example of the combined use of CTCA and CMR is shown in figure 4.

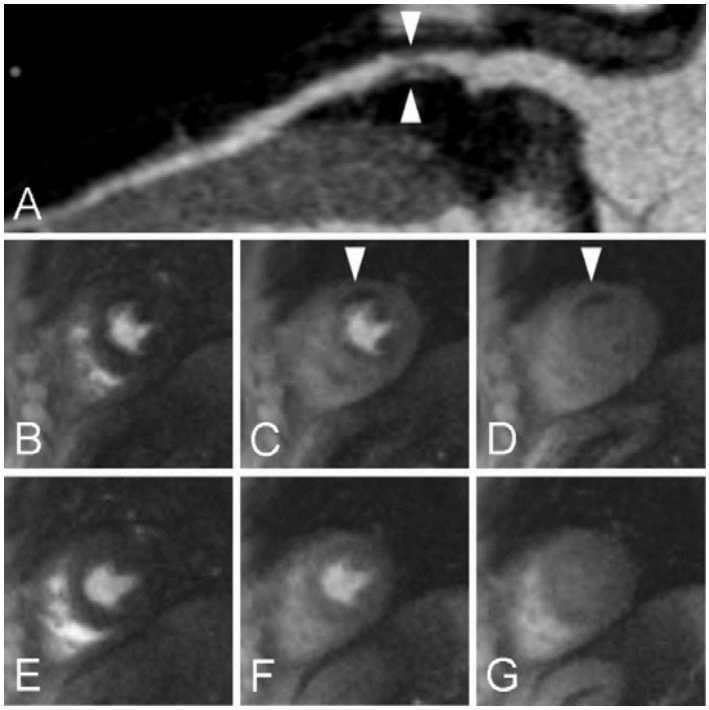

Figure 4. Images of a 58-year old man with atypical chest pain. CTCA image showing non-calcified atherosclerotic plaque in the proximal left coronary artery causing > 50% diameter stenosis (A, arrowheads). MR myocardial perfusion images on mid ventricular short axis level at 3 time points during first pass of a contrast bolus through right and left ventricle and perfusion of the myocardium (B-G). During adenosine-stress (B-D) a perfusion defect is visible in the anterior myocardial wall (B-D, arrowheads) that is not present at rest (E-G).

Outline of the thesis

In the current thesis we have investigated the relation between CMR and cardiac CT and the diagnostic yield of several algorithms using these techniques in patients with chest pain and low to intermediate pre-test probability of having significant CAD. In **chapter 2** we investigated the relationship between exercise electrocardiography (X-ECG) and functional and anatomical imaging modalities for the diagnostic evaluation of patients with suspected CAD. In **chapter 3** the positive predictive value (PPV) of computed tomography coronary angiography (CTCA) for the detection of significant coronary artery disease (CAD) was investigated in patients with low to intermediate pre-test probability CAD that were referred for non-invasive evaluation of chest pain. Furthermore, the influence of the composition of atherosclerotic plaque as detected by CTCA on the PPV was investigated. In **chapter 4** we investigated how anatomical findings on CTCA relate to functional findings on first pass magnetic resonance myocardial perfusion imaging in patients with chest pain and low to intermediate probability CAD. In **chapter 5** we investigated the combined use of cardiac CT and CMR for the diagnostic evaluation of patients with suspected CAD in clinical practice. In **chapter 6**, we described clinical outcome of patients that underwent both CTCA and CMR. In **chapter 7**, we investigated the incremental diagnostic value of dual bolus over single contrast bolus first pass magnetic resonance myocardial perfusion imaging for the absolute quantification of myocardial blood flow in patients with suspected CAD.

In **chapter 8**, general considerations are discussed and future perspectives are presented, that are illustrated by 3 case reports**.**

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