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Summary

Cardiovascular magnetic resonance imaging and computed tomography in patients with suspected coronary artery disease

Whereas the diagnostic evaluation of patients with suspected coronary artery disease (CAD) is part of the daily routine of cardiology practice, the conventional modalities for non-invasive detection of CAD have major limitations. Recently, cardiac computed tomography (CT) has been developed and is increasingly used in clinical practice. It is the first and only technique that can accurately visualize coronary anatomy non-invasively. 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. CMR is an accurate and robust method for quantification of ventricular volumes, function and regional myocardial scarring, and can accurately detect myocardial ischemia, without the use of ionizing radiation. In the present thesis the combined use of CTCA and CMR techniques was investigated in patients with low to intermediate probability of having significant CAD. Combining CT and CMR may provide the clinician a strategy to accurately evaluate coronary morphology and function non-invasively.

Chapter 1 provides an introduction to the non-invasive diagnostic work-up of patients with suspected CAD. It describes the most used diagnostic modalities for the non-invasive detection of CAD and their role in the ischemic cascade. Furthermore, basic scan protocols and recent results from diagnostic and prognostic studies of CT and CMR are presented.

In **chapter 2** the results of exercise electrocardiography (X-ECG) are compared with coronary calcium scoring, CT coronary angiography and CMR myocardial perfusion imaging (MRMPI) in patients with suspected CAD. Our results showed a lack of correlation between either X-ECG and CCS, CTCA and MRMPI. Particularly the sensitivity of X-ECG for detection of anatomically and hemodynamically relevant CAD was low. More than 50% of patients with normal X-ECG did have CAD on CTCA and 17% had myocardial ischemia. Furthermore, in over 20% of patients with inconclusive X-ECG, obstructive CAD or ischemia was observed. Our results showed that in contrast to X-ECG, CCS and CTCA did correlate to MRMPI.

Several studies have investigated the diagnostic performance of computed tomography coronary angiography (CTCA) for the detection of significant coronary artery disease (CAD). These studies were performed in patients who were already referred for invasive coronary angiography (ICA) and prevalence of significant CAD was high. Although the negative predictive value of CTCA was consistently high, a wide range of positive predictive values (PPV) was reported. Thus, the PPV of CTCA in patients that undergo CTCA as part of a clinical diagnostic evaluation remains unclear. In **chapter 3** the PPV of CTCA for the detection significant CAD was investigated in symptomatic patients with low to intermediate pre-test probability CAD, who were clinically referred for non-invasive evaluation of chest pain, but who were not yet referred for ICA. Overall, 65 out of 181 (35.9%) patients that underwent CTCA had obstructive CAD according to CTCA. The PPV for detection of significant CAD as defined by ICA per patient, per vessel and per

segment were 40.0% (95% CI: 30.6-50.2%), 31.3% (95% CI: 24.7-38.8%) and 25.5% (95% CI: 20.3-31.4%), respectively. Furthermore, we found that the PPV for detection of significant CAD in segments with non-calcified plaque was significantly higher than in segments with calcified plaque (50% versus 17%; $p=0.019$). We concluded that the PPV of CTCA for detection of significant CAD in patients with low to intermediate probability CAD, that are clinically referred for non-invasive evaluation of chest pain is markedly lower than generally reported. Thus, direct referral of all patients who have obstructive CAD on CTCA for ICA would lead to a large number of unnecessary invasive diagnostic procedures. Therefore, additional non-invasive functional testing should be performed when obstructive CAD is observed.

Chapter 4 describes how CTCA findings relate to adenosine stress and rest MRMPI findings in patients with chest pain and low to intermediate probability CAD. The main result was that only 42.3% (22/52) of patients with obstructive CAD according to CTCA, had myocardial ischemia on MRMPI. Conversely, most patients without CAD on CTCA had normal myocardial perfusion on MRMPI. Thus, CTCA can reliably rule-out CAD, however, detection of hemodynamic significant CAD is limited. On the other hand, normal myocardial perfusion does not exclude any CAD. These findings show the complementary role of CTCA and myocardial perfusion imaging in the evaluation of suspected CAD. CTCA can reliably detect and rule out CAD, and myocardial perfusion imaging subsequently assesses the functional relevance of CAD. Furthermore, this study showed the feasibility of the combined use of CTCA and MRMPI: in 145 of 154 patients (94.2%) both CTCA and MRMPI were performed successfully.

In **chapter 5** the usefulness of a combined work-up using cardiovascular magnetic resonance imaging (CMR) and cardiac computed tomography (CT) for the diagnostic evaluation of patients with low to intermediate pre-test probability of CAD was investigated. Patients ($n=192$) with low or intermediate pre-test probability of CAD underwent CTCA and CMR. All patients with obstructive CAD on CTCA and/or myocardial ischemia on CMR were referred for invasive coronary angiography (ICA) and fractional flow reserve was measured in case of intermediate lesions (30-70% diameter stenosis) on ICA. We found that the combined strategy (additional CMR when CTCA detects obstructive CAD) significantly improved specificity and overall accuracy (94% and 91%) for the detection of significant CAD compared with their use as a single technique (CTCA 39% and 57%, $p<0.0001$; CMR 82% and 83%, $p=0.016$). Furthermore, the combination of CTCA and CMR provided an alternative diagnosis in 19 patients. Therefore, we concluded that the combined use of CTCA and CMR significantly improved specificity and overall diagnostic accuracy for the detection of significant CAD, and allowed the detection of alternative (extra-) cardiac disease in patients without significant CAD.

In **Chapter 6** clinical outcome was explored of patients with suspected CAD in relation to CCS, CTCA and CMR, each as a single technique, and as part of a stepwise protocol.

During a mean follow-up interval of 18 ± 5 months, 25 patients experienced an event: 23 revascularizations, 1 myocardial infarction and 1 death. Overall, multivariable Cox regression analysis showed a significant improvement in predictive value by the combination of CTCA and CMR versus CTCA or CMR alone (chi-square change 17.06, $p < 0.001$ or 8.06, $p = 0.005$). However, CMR had no incremental predictive value in patients without obstructive CAD on CTCA ($p = 0.74$).

In **chapter 7** the diagnostic performance for detection of significant CAD of absolute quantitative perfusion values is investigated using two different contrast injection methods during adenosine stress and rest magnetic resonance myocardial perfusion imaging. The novel dual contrast bolus technique may correct for saturation effects due to the non-linear relation between contrast concentration and signal intensity at high contrast concentrations. The dual bolus technique resulted in lower mean perfusion values, that are more in line with values reported in previous studies. However, it had no incremental diagnostic value over the single bolus technique for the detection of significant CAD.

In **chapter 8** general considerations and future perspectives are discussed and illustrated by three case reports.

In this thesis we propose a new diagnostic workup of patients with chest pain and low or intermediate likelihood of having significant CAD. CTCA is used as first line technique that can reliably rule out significant CAD. When obstructive CAD is detected by CTCA, patients will undergo CMR for the evaluation of the hemodynamically significance of CAD. This work-up improves diagnostic accuracy for detection of significant CAD, reduces the number of patients that will undergo myocardial perfusion imaging and allows the detection of alternative (extra-) cardiac causes of chest pain, without the cost of additional radiation. However, further research is needed to investigate whether this new strategy improves risk stratification when compared to conventional diagnostic strategies, and is more cost-effective. Furthermore, with the ongoing development of CT and CMR, their role within the work-up of patients with suspected CAD may evolve in the future.