Multimodality Imaging of Anatomy and Function in Coronary Artery Disease

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Summary and Conclusion

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The general introduction (**Chapter 1)** of this thesis provides an overview of the different modalities that are available for diagnosis of coronary artery disease (CAD). The individual strengths and limitations as well as the current accuracies - based on pooled analyses of the literature when available - of each imaging modality are described, followed by the outline of the thesis.

Part I

The first part of the thesis focuses on the recently introduced technique Multi-Slice Computed Tomography (MSCT). MSCT is a rapidly developing technique that allows direct noninvasive visualization of the coronary arteries. In **Chapter 2**, the technical background of performing noninvasive coronary angiography with this novel technique is described. Data acquisition and post-processing protocols for optimal image quality and data evaluation are discussed. In addition, the potential applications of MSCT coronary angiography are outlined.

Subsequently, the diagnostic accuracy of this novel technique in the detection of significant CAD (defined as 50% luminal narrowing or more) as compared to conventional coronary angiography is explored in **Chapters 3-5**. In **Chapter 3**, the diagnostic accuracy of 16-slice MSCT to detect significant stenosis was evaluated in 45 patients presenting with suspected or known CAD. A total of 94% of native coronary artery segments could be evaluated with MSCT, whereas 85% of grafts and 79% of coronary stents were interpretable. For all segments, overall sensitivity, specificity, and positive and negative predictive values were 85%, 89%, 71%, and 95%, respectively. In addition to evaluation of the coronary arteries, left ventricular ejection fraction (LVEF) was evaluated and compared to 2D-echocardiography, which revealed a close correlation between these modalities. With regard to the high specificity and negative predictive value observed, it was concluded that 16-slice MSCT may be useful as a noninvasive modality to rule out significant stenosis. In addition, LVEF, being an important prognostic marker, may be evaluated with high accuracy. More recently, 64-slice MSCT has become available with the simultaneous acquisition of 64 rather than 16-slices per rotation as well as with improved rotation times. **Chapter 4** describes the initial results obtained with this scanner. A sensitivity and specificity of 94% and 97%, respectively, were obtained on a patient basis. In conclusion, the study confirmed - in line with previous investigations - that 64-slice MSCT enables accurate noninvasive evaluation of significant coronary artery stenoses. Finally, a meta-analysis of the available literature on noninvasive coronary imaging with either MSCT or Magnetic Resonance Imaging (MRI) was performed. In **Chapter 5** the results from this meta-analysis are described. Comparison of sensitivities and specificities revealed significantly higher values for MSCT (weighted average 85% and 95%) as compared with MRI (weighted average 72%, and 87%). In addition, a significantly higher odds ratio (16.9-fold) for the presence of significant stenosis was observed for MSCT as compared with MRI (6.4-fold) ($P < 0.0001$). Accordingly, the results of this meta-analysis of the available literature on noninvasive coronary angiography with MRI and MSCT indicated that MSCT has currently a significantly higher accuracy to detect or exclude significant CAD.

Part II

In the second part of the thesis, the potential use of MSCT and MRI is explored in subpopulations in order to identify those patient populations that may or may not benefit from these techniques. For example, patients with certain risk factors for CAD may benefit from early identification of CAD followed by targeted atherosclerotic treatment. However, it is important to establish beforehand whether the presence of these risk factors do not have any negative influence on the diagnostic performance of MSCT. In **Part II A**, therefore, the diagnostic performance of 4-and 16-slice MSCT was explored in the setting of different risk factors. In **Chapter 6**, the potential of MSCT coronary angiography was evaluated in patients with type 2 diabetes. A total of 86% of segments was interpretable with MSCT. In these segments, sensitivity and specificity for detection of coronary stenoses were 95%. Including the uninterpretable segments, sensitivity and specificity were 81% and 82%, respectively. In addition, no significant difference was observed between LVEF values obtained by MSCT and 2D-echocardiography, while agreement in the assessment of regional contractile function was also excellent (91%). Accordingly, no major effect of type 2 diabetes on the diagnostic performance of MSCT was revealed, indicating that this technique may allow optimal identification of high-risk patients in this population. In **Chapter 7**, MSCT was applied in patients with hypertension. A total of 88% coronary artery segments could be evaluated with MSCT. Sensitivity and specificity for the detection of significant stenoses were 93% and 96%. On a per-patient basis, MSCT was accurate in 90% of patients. The results suggest that in patients with hypertension, MSCT may be applied for noninvasive triage of patients. Finally in **Chapter 8**, the effect of gender and various risk factors for CAD (including type 2 diabetes, hypertension, obesity, smoking and hypercholesterolemia) on the diagnostic accuracy of 16-slice was explored in 197 patients. Patients were enrolled in the Erasmus Medical Center Rotterdam and the Leiden University Medical Center. Overall, a sensitivity and specificity of 99% and 86%, respectively, on a patient level were demonstrated. Among the various subsets of patients, similar values were observed, with no statistical differences, indicating a high diagnostic accuracy of MSCT coronary angiography, regardless of gender and risk factors.

In **part II B**, patients with a history of revascularisation were studied. In this population, noninvasive imaging may be more challenging as compared to patients with suspected CAD due to the presence of stents and surgical clips, resulting in metal artefacts. In addition, the presence of extensive atherosclerosis may also pose substantial difficulties. In **Chapter 9**, the feasibility of 16-slice MSCT to evaluate patency of intracoronary stents was investigated in patients referred for conventional coronary angiography. For each stent, assessability was determined and related to stent type and diameter. Subsequently, the presence of significant restenosis was determined in the evaluable stents as well as peri-stent lumina. Of 65 stents, 50 (77%) were considered assessable. Uninterpretable stents tended to have a thicker strut thickness (≥ 140 μm) and/or a smaller diameter (≤ 3.0 mm). In the evaluable stents, a sensitivity and specificity of 78% and 100%, respectively, were obtained. Sensitivity and specificity for the detection of peri-stent stenosis were 75% and 96%, respectively. In conclusion, in stents with a larger diameter and relatively thin struts, MSCT may be useful in the assessment of stent patency and may function as a gatekeeper prior to invasive diagnostic procedures.

The expectation of improved assessability of coronary stents with 64-slice MSCT was tested in **Chapter 10**. State-of-the-art imaging and evaluation protocols were applied in 182 patients presenting with a total of 192 stents. MSCT images obtained by 64-slice MSCT (either using a Siemens Sensation or Toshiba Aquilion) were evaluated by experienced observers at each center for the presence of significant in-stent restenosis. Only stents with a diameter ≥ 2.5 mm were included. Ninety-three percent of stents were of good diagnostic quality. In interpretable stents, high sensitivity and specificity to identify in-stent restenosis were observed. Accordingly, in stents with a larger diameter, in-stent restenosis can be evaluated with 64-slice MSCT with good diagnostic accuracy. In particular, a high negative predictive value of 99% was observed indicating that 64-slice MSCT may be most valuable as a noninvasive method of excluding in-stent restenosis.

In **Chapter 11**, the performance of 64-slice MSCT in the assessment of in-stent restenosis was evaluated in more detail. In 50 patients, 64-slice MSCT was performed in addition to conventional coronary angiography with quantitative coronary angiography (QCA). For each stent, assessability was determined and related to stent characteristics and heart rate. In the interpretable stents, the presence of significant (≥50%) restenosis was determined. Since restenosis may frequently occur at the stent borders, also peri-stent lumina (5.00 mm proximal and distal to the stent) were evaluated. Of 76 stents, 86% were determined assessable. Increased heart rate and overlapping positioning were found to be associated with increased stent uninterpretability, whereas stent location and strut thickness were not. In the interpretable stents, the presence or absence of significant (≥50%) in-stent restenoses was correctly detected in all stents. Sensitivity and specificity for the detection of significant (≥50%) peri-stent stenosis were 100% and 98%, respectively. In selected patients with previous stent implantation, 64-slice MSCT may allow accurate evaluation of in-stent and peri-stent stenosis.

Although percutaneous coronary intervention is increasingly performed in the treatment of obstructive CAD, a considerable portion of patients still receives coronary bypass surgery. In **Chapter 12**, a high-resolution, phase contrast MRI sequence for quantifying flow in small and large vessels was validated. In addition, its feasibility to measure flow in coronary artery bypass grafts was demonstrated. For this purpose, a breath-hold, echo planar imaging (EPI) sequence was developed and validated in a flow phantom using a fast field echo (FFE) sequence as reference. In 17 volunteers aortic flow was measured using both sequences. In 5 patients flow in the left internal mammary artery (LIMA) and aorta was measured at rest and during adenosine stress, and coronary flow reserve (CFR) was calculated; in 7 patients, vein graft flow velocity was measured. In the flow phantom measurements, the EPI sequence yielded an excellent correlation with the FFE sequence, while also aortic volume flow in healthy volunteers correlated well with only a minor overestimation. It was feasible to measure flow velocity in the LIMA and vein grafts of the 12 patients.

Part III

Based on the consistently high negative predictive value of MSCT coronary angiography, the technique has been proposed as a suitable alternative for first-line evaluation in patients presenting with suspected CAD. However, functional imaging modalities have traditionally been used for this

purpose. As a result, the presence and extent of ischemia, i.e. the hemodynamical consequences of a lesion, have served as the gatekeeper for referral to conventional coronary angiography. In contrast, MSCT coronary angiography provides direct information on coronary anatomy. Accordingly, in order to fully appreciate both the potential and limitations of this new technique as well as to allow optimal integration, its performance needs to be evaluated not only against conventional coronary angiography but also against functional imaging.

In **Chapter 13**, an update of the various noninvasive modalities, including both anatomical as well as functional modalities, is provided. Their values in both the diagnosis of obstructive CAD and prognostification are discussed. In addition, a potential algorithm for integration of anatomical imaging with MSCT and functional imaging is proposed.

In order to design and support such algorithms, the relationship between noninvasive coronary angiography with MSCT and myocardial perfusion imaging (MPI) needs to be determined. Therefore, in **Chapter 14**, a total of 114 patients, presenting with an intermediate pre-test likelihood of CAD, underwent both MSCT coronary angiography and myocardial perfusion imaging (MPI) using gated SPECT. An excellent agreement was observed between normal coronary arteries on MSCT and the presence of normal myocardial perfusion on gated SPECT (90%). In contrast, only 50% of patients with a significant stenosis on MSCT displayed abnormal perfusion during gated SPECT. Accordingly, an abnormal MSCT does not imply the presence of a hemodynamically relevant stenosis. As knowledge of ischemia is needed to determine further management and decide between aggressive intervention or conventional therapy, functional testing appears necessary following an abnormal MSCT scan. On the other hand, CAD could be ruled out by MSCT in only 46% of patients with a normal perfusion study, indicating that a normal MPI cannot rule out extensive atherosclerosis. Combination of both techniques, either by integrated or sequential imaging, may therefore be preferred and allow more precise cardiac assessment. This current change in paradigm - namely the shift from detection of ischemia to detection of (sub)clinical atherosclerosis - is further discussed in **Chapter 15.**

In **Chapter 16**, the relation between anatomical imaging, using both MSCT calcium scoring and noninvasive coronary angiography, and MPI was assessed in an unselected population, including patients with known CAD. Analysis of data on a regional basis revealed that in coronary arteries with a calcium score of 10 or less, the corresponding myocardial perfusion was normal in 87%. In coronary arteries with extensive calcifications (calcium score > 400), the percentage of vascular territories with normal myocardial perfusion was substantially lower, 54%. Similarly, coronary arteries without detectable atherosclerosis as well as coronary arteries with non-obstructive atherosclerosis were generally found to be associated with normal myocardial perfusion in the corresponding vascular territory (89%).

In contrast, the percentage of normal SPECT findings was significantly lower in coronary arteries with obstructive lesions (59%) or with total or subtotal occlusions (8%). Nonetheless, only 48% of vascular territories with normal perfusion corresponded to normal coronary arteries on MSCT angiography, whereas insignificant and significant stenoses were present in, respectively, 40% and 12% of corresponding coronary arteries.

These discrepant findings were further investigated in **Chapter 17.** In a subset of patients, the discrepancy between MPI and MSCT was compared to invasive imaging, not only of the coronary artery lumen (using invasive coronary angiography) but also of the vessel wall (using intravascular ultrasound, IVUS). A good agreement between modalities was observed in patients with abnormal MPI. However, a normal MPI study was in most patients associated with an abnormal MSCT study. In these patients only minimal luminal stenosis was observed on QCA (26.5%) as well. Considerable plaque burden (58%), however, was revealed by IVUS imaging, yet without luminal compromise (average minimal luminal area 5.7 mm^2). From the chapter was concluded that in patients with discrepant MSCT and MPI findings, the detected atherosclerosis may be located mainly in the vessel wall, rather than extending into the coronary lumen.

Part IV

A particular feature of MSCT is that it allows visualization of not only luminal narrowing but also of the coronary vessel wall. While this may lead to discrepant results with other imaging modalities as described in Part III, knowledge of the presence and extent of atherosclerosis may eventually become an advantage of MSCT.

In **Chapter 18** the hypothesis that MSCT may detect differences in plaque composition and distribution between patients with stable CAD versus patients presenting with acute coronary syndromes (ACS) was tested. In patients with stable CAD, the majority of lesions were calcified (89%), whereas in patients with ACS, a greater proportion of noncalcified (18%) or mixed (36%) lesions was noted. Moreover, even in non-culprit vessels, multiple noncalcified plaques were detected, indicating the presence of diffuse rather than focal atherosclerosis in ACS.

In **Chapter 19**, the influence of type 2 diabetes on MSCT plaque characteristics, including plaque extent and composition was evaluated in 215 patients, of whom 40% with type 2 diabetes. Significant differences in plaque characteristics were observed and the presence of diabetes was demonstrated to correlate with the number of diseased segments and the number of nonobstructive, noncalcified, and calcified plaques. Diabetes was associated with increased coronary plaque burden as well as more noncalcified and calcified plaques and less mixed plaques. Since MSCT may provide an estimate of coronary plaque burden as well as distinction in atherosclerotic patterns between various clinical presentations, this information obtained with MSCT may be useful for risk stratification. **Chapter 20** describes the observations in 100 patients who were followed for coronary events (including cardiac death, nonfatal myocardial infarction, unstable angina requiring hospitalisation, and revascularisation) after a baseline MSCT examination. During a mean follow-up of 16 months, 33 events occurred in 26 patients. In patients with normal coronary arteries on MSCT, the first-year event rate was 0% versus 30% in patients with any evidence of CAD on MSCT. The observed event rate was highest in the presence of obstructive lesions (63%) and when obstructive lesions were located in the left main (LM)/left anterior descending (LAD) coronary arteries (77%). Nonetheless, an elevated event rate was also observed in patients with nonobstructive CAD (8%). In multivariate analysis, significant predictors of events were the presence of CAD, obstructive CAD, obstructive CAD in LM/LAD, number of segments with plaques, number of segments with obstructive plaques, and

number of segments with mixed plaques. From this chapter it was concluded that MSCT coronary angiography provides independent prognostic information over baseline clinical risk factors in patients with known and suspected CAD. Of particular importance, an excellent prognosis was noted in patients with a normal MSCT, supporting safe rule-out of CAD with this technique.

Part V

In the final part of the thesis, non-coronary applications of MSCT and MRI are described. Delayed enhancement MRI allows precise delineation of infarcted myocardium including assessment of transmural extent. In **Chapter 21**, a head-to-head comparison was performed between visual and quantitative analyses of infarct transmurality in 27 patients with long-term ischemic LV dysfunction and previous infarction. In addition, infarct transmurality was related to the severity of wall motion abnormalities at rest. Both cine MR imaging (to assess regional wall motion) and contrast enhanced (ce) - MR imaging were performed and visually analysed using a 17-segment model for wall motion and segmental infarct transmurality. Quantification of transmurality was performed with threshold analysis. The agreement between visual and quantitative analyses was excellent: 90% of segments (kappa 0.86) were categorised similarly by visual and quantitative analyses. Infarct transmurality paralleled the severity of contractile dysfunction; 96% of normal or mildly hypokinetic segments had infarct transmurality ≤25%, whereas 93% of akinetic and dyskinetic segments had transmurality >50% on visual analysis. In conclusion, visual analysis of ce-MR imaging studies may be sufficient for assessment of transmurality of infarction.

Information on myocardial infarct tissue may also be derived from MSCT. As a 3D data set is acquired during ECG gating, images can be reconstructed in the short-axis orientation throughout the cardiac cycle. In addition, imaging is performed during a bolus administration of contrast agent, resulting in images during first-pass. As a result, areas of reduced myocardial perfusion can be identified as hypodense areas on the MSCT images. The purpose of **Chapter 22** was to evaluate the potential of MSCT to provide a comprehensive cardiac assessment, with evaluation of LV function and perfusion in addition to coronary anatomy. In 21 patients with previous infarction, MSCT was performed in addition to conventional coronary angiography (coronary anatomy) and gated SPECT imaging (perfusion and function). In this population, observed sensitivity and specificity for detection of stenoses were 91% and 97% with 98% of segments being interpretable on MSCT. Excellent agreement was observed for assessment of LVEF and regional wall motion between MSCT and SPECT. With regard to perfusion, MSCT correctly identified a resting perfusion defect in 93%, whereas the absence of perfusion defects was correctly detected in 98% of segments. LV function measurements were further validated in **Chapter 23**. Measurements of LV volumes and LVEF were compared to 2D-echocardiography. Linear regression analysis showed excellent correlations between the 2 techniques, although LVEF was slightly overestimated with MSCT. Finally, in **Chapter 24**, a novel application of MSCT coronary angiography, namely the visualization of the cardiac venous system, was evaluated. For successful LV lead implantation in cardiac resynchronization therapy (CRT), knowledge of venous anatomy may be useful. The presence of the coronary sinus tributaries was evaluated in a total of 100 patients of whom 28 control patients, 38 patients with significant CAD, and 34 patients with a history of myocardial

infarction. While the coronary sinus and posterior interventricular vein were identified in all patients, a left marginal vein (LMV) was significantly less frequently observed in patients with a history of infarction as compared with control patients and CAD patients (27% vs. 71% and 61%, respectively). None of the patients with lateral wall infarction and only 22% of patients with anterior wall infarction showed a LMV on MSCT in. Accordingly, there appears to be a considerable variation in venous anatomy. Patients with a history of myocardial infarction showed less frequently a LMV, which may hamper optimal LV lead positioning in CRT implantation.

Conclusion

Various modalities are available in the diagnostic and prognostic evaluation of patients presenting with known or suspected CAD. A particularly rapidly expanding technique is noninvasive coronary angiography with MSCT. During the past few years, noninvasive coronary angiography with this technique has witnessed an enormous development. In comparison to invasive coronary angiography, the technique has been demonstrated to allow accurate detection of significant coronary stenoses and currently outperforms noninvasive coronary angiography with MRI. Due to the high negative predictive value, the most important contribution of the technique will lie in the noninvasive exclusion of CAD in patients presenting with suspected CAD and intermediate pre-test likelihood. Although imaging in populations such as patients with previous stent placement appears to be more challenging, promising results have been obtained in these populations as well.

However, it remains important to realize that only half of the significant lesions on MSCT appear to have hemodynamical consequences. These observations indicate that the presence of coronary atherosclerosis with luminal obstruction does not invariably imply the presence of ischemia. Accordingly, a noninvasive angiographic imaging technique such as MSCT cannot be used to predict the hemodynamical importance of observed lesions. In patients with borderline stenosis or limited image quality on MSCT, therefore, functional testing will remain necessary to determine the presence of ischemia. This can be performed by nuclear imaging, stress echocardiography or MRI. Moreover, the latter may allow measurements of coronary flow in coronary bypass grafts.

One of the advantages of MSCT on the other hand, is the fact that the technique allows detection of CAD at a far earlier stage than functional imaging. Initial investigations even suggest that MSCT may distinguish different plaque characteristics between various presentations. Potentially, this information could be useful for risk stratification. Finally, in addition to information on the coronary arteries, also other non-coronary information can be derived from the MSCT examination. LV function can be evaluated with high accuracy while also information on the cardiac venous system can be obtained.

With regard to daily clinical management in patients presenting with (suspected) CAD, integration of MSCT coronary angiography with functional imaging techniques may potentially be most beneficial. This will allow accurate exclusion as well as earlier detection of CAD in combination with knowledge of ischemia. However, it is important to realize that available data are currently scarce and investigations supporting improved outcome as well as cost-effectiveness of algorithms incorporating both MSCT coronary angiography and functional testing are eagerly awaited.