Imaging of coronary atherosclerosis with multi-slice computed tomography
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Summary and Conclusions

SUMMARY AND CONCLUSIONS

In the introduction of this thesis (**Chapter 1**) an overview of the applications of multi-slice computed tomography (MSCT) in imaging of coronary artery disease (CAD) is provided. The technical parameters, current applications as well as strengths and limitations of the technique are discussed. Finally, the outline of the thesis is provided.

Part I

The ability of MSCT to demonstrate obstructive atherosclerotic lesions in the coronary arteries was explored in the first part of the thesis. The diagnostic accuracy of non-invasive MSCT coronary angiography in the detection of obstructive coronary artery lesions (≥50% luminal narrowing) as compared with conventional coronary angiography is described in **Chapters 2** to **4**. In **Chapter 2**, the diagnostic accuracy of 64-slice MSCT in the detection of obstructive CAD using conventional coronary angiography as the gold standard was explored in 60 patients with high pre-test likelihood of CAD. In total, 99% of coronary artery segments were of sufficient image quality. The sensitivity and specificity of MSCT to demonstrate obstructive lesions on segmental level were 85% and 97%, respectively. On a patient level, sensitivity, specificity, positive and negative predictive values were 94%, 97%, 97%, and 93%, respectively. It was concluded that 64-slice MSCT enables the accurate and non-invasive evaluation of obstructive coronary artery stenoses.

In **Chapter 3**, the influence of the patient's gender on the diagnostic accuracy of 64-slice MSCT to detect obstructive coronary lesions was investigated in 51 men and 52 women with known and suspected CAD. On segmental level, 96% coronary segments were of sufficient image quality in women and 97% segments were interpretable in men. On a patient level, the sensitivity in women and men was 95% (95% CI 87%-100%) versus 100%, the specificity was 93% (95% CI 83%-100%) versus 89% (95% CI 74%-100%), respectively. Accordingly, the findings of the study confirmed the high diagnostic accuracy of 64-slice MSCT coronary angiography both in female and in male patients.

Since the accumulation of calcium in the coronary arteries is one of the most important factors which hamper the image quality of MSCT coronary angiography, the impact of coronary calcium on the diagnostic accuracy of MSCT coronary angiography was investigated in **Chapter 4**. This impact was compared between patients examined with the previous 16-slice MSCT scanner (41 patients) and with a more recent 64-slice MSCT scanner (60 patients). MSCT scans were analyzed with invasive coronary angiography as a standard of reference. On segmental level, the percentage of false negative segments in the groups with Agatston calcium scores 0-100, 101-400 and >400 with 16-slice MSCT were 0%, 5.3%, 2.9% ($p<0.05$), other comparisons of false positive and false negative segments both with 16- and with 64-slice MSCT were not significant. The sensitivity and specificity to detect obstructive lesions on a vessel and a patient level with 16- and 64-slice MSCT were not significantly different in different calcium score groups. In conclusion, a slight impact of coronary calcium was observed on the diagnostic accuracy of 16-slice MSCT coronary angiography on segmental level with no significant impact on a vessel and a patient level. No significant impact of coronary calcium was observed on the diagnostic accuracy of 64-slice MSCT coronary angiography on segmental, vessel and patient levels.

As patients having obstructive coronary artery lesions are frequently managed with percutaneous coronary interventions with the implantation of stents, a state-of-the-art 64-slice MSCT scanner could possibly be used to non-invasively assess coronary stent patency after implantation. Accordingly, the diagnostic accuracy of 64-slice MSCT to diagnose in-stent restenosis in 50 patients was assessed in **Chapter 5**. In total, 86% stents were determined to be assessable. All significant in-stent restenoses were detected, and the absence of significant in-stent restenosis was correctly identified in all stents, resulting in sensitivity and specificity of 100%. The negative predictive value was particularly high (100%) indicating that 64-slice MSCT may be a valuable non-invasive method to exclude in-stent restenosis.

Since both exercise testing and MSCT may be used for initial detection of CAD in patients presenting with suspected CAD, a head-to-head comparison between signs of ischemia during bicycle exercise testing and coronary atherosclerosis on MSCT was performed in **Chapter 6**. In total, 201 patients underwent exercise testing, followed by 64-slice MSCT, whereas a subgroup of 63 (31%) patients also underwent conventional coronary angiography. In 178 patients with interpretable examinations, coronary calcium score was identical in patients with a positive (11 (0-343)) and a negative exercise test (18 (0-335), p=NS). The prevalence of non-obstructive CAD on MSCT was the same in 2 patients groups (36% of patients with a positive versus 38% of patients with a negative exercise test, p=NS). Although obstructive CAD was observed on MSCT in 42% of patients having a positive exercise test, obstructive lesions were also present in 27% of patients without ischemia on exercise testing. The findings were confirmed by conventional coronary angiography. In conclusion, no correlation was observed between ischemia on exercise testing and both calcium scoring and non-obstructive CAD on MSCT. A large proportion of obstructive lesions on MSCT were not demonstrated on exercise testing. Accordingly, MSCT may provide additional information on CAD as compared with bicycle exercise testing.

Part II

The second part of this thesis focused on characterization of coronary atherosclerotic plaque extent and composition on MSCT.

In addition to demonstration of obstructive coronary artery lesions, MSCT coronary angiography can also provide data on the presence of non-obstructive plaques and to some extent on plaque composition. Accordingly, this information may potentially be used for the assessment of patient risk for future cardiovascular events. In **Chapter 7**, the prognostic value of MSCT coronary angiography was assessed in 100 patients with known or suspected CAD. Patients were followed for the occurrence of cardiovascular events (cardiac death, non-fatal myocardial infarction, unstable angina requiring hospitalization, revascularization). During a mean follow-up of 16 months, 33 events occurred in 26 patients. In patients with normal coronary arteries on MSCT, first year event rate was 0% versus 30% (24/80) in patients with any evidence of CAD on MSCT. Observed event rate was highest in the presence of obstructive lesions (63% (20/32)) and when obstructive lesions were located in the left main/left anterior descending (LAD) coronary arteries (77% (18/23)). Nonetheless, elevated event rate was also observed in patients with non-obstructive CAD (8% (4/48)). In conclusion, MSCT coronary angiography provides independent prognostic information over baseline clinical risk factors in patients with known and suspected CAD. Excellent prognosis was noted in patients with a normal MSCT.

In order to get a better impression about coronary plaque composition on MSCT, plaque observations on MSCT were compared to a more accurate invasive modality intravascular ultrasound radiofrequency data analysis (virtual histology intravascular ultrasound (VH IVUS)). In **Chapter 8**, a head-to-head comparison of plaque observations with MSCT to VH IVUS was performed. Fifty patients underwent 64-slice MSCT followed by VH IVUS. Agatston calcium score was evaluated on MSCT in coronary segments where IVUS was performed. Plaques were classified on MSCT as non-calcified, mixed and calcified. Four plaque components were identified on VH IVUS (fibrotic, fibro-fatty, necrotic core, dense calcium) as well as the presence of thin cap fibroatheroma (TCFA) in the plaques was assessed. A moderate correlation was observed between Agatston calcium score on MSCT and calcium volume on VH IVUS (r=0.69, p<0.0001). In total, 168 coronary plaques were evaluated (48 (29%) non-calcified, 71 (42%) mixed, 49 (29%) calcified). As compared with calcified plaques, non-calcified plaques contained more fibrotic (60.90±9.21% versus 54.60±8.33%, p=0.001) and fibro-fatty tissues (28.11±13.03% versus 21.37±9.75%, p=0.006) on VH IVUS. Mixed and calcified plaques contained more dense calcium as compared with non-calcified plaques (7.61±8.94% versus 2.68±3.01%, p=0.001; 10.18±6.71% versus 2.68±3.01%, p<0.001, respectively). TCFA were most frequently observed in mixed plaques, as compared with non-calcified and calcified plaques (32%, 13%, 8%, p=0.002, respectively). It was concluded that a good correlation was observed between calcium quantification on MSCT and VH IVUS. Plaque classification on MSCT paralleled plaque composition on VH IVUS, although VH IVUS provided more precise plaque characterization. Mixed plaques on MSCT were associated with high risk features on VH IVUS.

In **Chapter 9**, the hypothesis that different coronary plaque patterns (plaque extent and composition) may be observed both on MSCT and VH IVUS in patients presenting with acute coronary syndromes (ACS) and stable CAD was tested. Twenty five patients with ACS and 25 patients with stable CAD underwent 64-slice MSCT followed by VH IVUS in 48 (96%) patients. In ACS patients, 32% of plaques were non-calcified on MSCT and 59% were mixed. In patients with stable CAD, completely calcified lesions were more prevalent (61%). On VH IVUS, the percentage of necrotic core was higher in the plaques of ACS patients (11.16±6.07% versus 9.08±4.62% in stable CAD, p=0.02). In addition, thin cap fibroatheroma were more prevalent in ACS patients (32% versus 3% in patients with stable CAD, p<0.001) and were most frequently observed in mixed plaques on MSCT. Plaque composition both on MSCT and VH IVUS was identical between culprit and non-culprit vessels of ACS patients. In conclusion, differences in plaque characterization were demonstrated between patients with ACS and stable CAD on MSCT. Plaques of ACS patients showed features of vulnerability to rupture on VH IVUS.

Type 2 diabetes is an established risk factor of CAD. Accordingly, diabetic patients have a higher risk for developing cardiovascular events. This higher risk may be related to differences in coronary plaque extent and composition. Accordingly, the influence of type 2 diabetes on coronary plaque patterns on MSCT was assessed in **Chapters 10** and **11**. In **Chapter 10**, MSCT was performed in 215 patients (40% with type 2 diabetes).

Significantly more diseased coronary artery segments were observed in diabetic patients compared with non-diabetic patients. In particular, more non-obstructive plaques were observed in the presence of type 2 diabetes. Relatively more non-calcified, calcified and less mixed plaques were observed in diabetic patients. Thus, MSCT may be used to identify differences in coronary plaque characteristics, which may be useful for patient risk stratification.

In **Chapter 11**, coronary plaque patterns were explored in diabetic patients with higher pre-test likelihood of obstructive CAD as compared with the previous study, who were referred for invasive coronary angiography in combination with IVUS. In a population of 60 patients (19 patients with type 2 diabetes), diabetic patients showed more plaques on MSCT. On gray-scale IVUS, diabetes was associated with a larger plaque burden. Concerning plaque composition, diabetes was associated with more calcified plaques on MSCT, whereas relatively more fibrocalcific plaques were observed in diabetic patients on VH IVUS. In conclusion, particular patterns of coronary atherosclerosis were identified in diabetic patients on MSCT, which were paralleled by the findings on invasive VH IVUS.

Finally, coronary plaque patterns were evaluated in 59 men and 34 women in relation to age using MSCT, gray-scale IVUS and VH IVUS in **Chapter 12**. Coronary plaque patterns were compared between men and women in 2 age groups (<65 and ≥65 years old). In younger men, more plaques were observed on MSCT as compared with younger women, whereas a larger plaque burden was observed on gray-scale IVUS. Similarly, in younger men more mixed plaques were observed on MSCT as compared with younger women, whereas a larger arc of calcium was detected on gray-scale IVUS. On VH IVUS, the prevalence of thin cap fibroatheroma was higher in younger men (31% versus 0%). No differences in plaque patterns were observed in older men and women. Thus, a more extensive atherosclerosis and more calcified lesions were observed in men as compared with women both on non-invasive MSCT and on invasive gray-scale and VH IVUS. Moreover, these differences were predominantly present in younger patients and were lost in older patients.

Conclusions

The improvement of technical parameters of MSCT scanners during the past decade has been paralleled by a rapid improvement in image quality and diagnostic accuracy of non-invasive MSCT coronary angiography. Non-invasive coronary angiography with state-of-the-art 64-slice technology allows accurate detection of obstructive coronary artery lesions as compared with conventional coronary angiography. In particular, the negative predictive value of MSCT coronary angiography is extremely high. Accordingly, the technique may be used for non-invasive exclusion of obstructive coronary artery lesions in patients presenting with suspected CAD. In addition, the diagnostic accuracy of 64-slice MSCT coronary angiography is similar in men and women. Whereas calcium accumulation was an important factor hampering image quality of coronary angiography with previous scanner generations, the influence of coronary artery calcium seems to decrease when images are acquired with 64-slice scanner. Promising results were demonstrated in imaging of coronary artery stents with 64-slice MSCT. In comparison to exercise testing (which is frequently used as a first-line test to exclude CAD), MSCT provides more detailed information on CAD.

In addition to the demonstration of obstructive coronary artery lesions, MSCT also allows detection of non-obstructive CAD, as well as characterization of coronary plaque composition. Initial observations, including comparisons with more accurate invasive techniques, suggest that MSCT may allow detection of different coronary plaque patterns in patients with different clinical presentations. Potentially, this information may be useful in the assessment of patient risk for cardiovascular events. Nevertheless, as the technique is still in its early stage of development and as the current observations on imaging of coronary atherosclerosis with MSCT are scarce, more data, including follow-up, are needed before imaging of coronary atherosclerosis with MSCT can be applied in clinical practice.