Imaging of coronary atherosclerosis and vulnerable plaque

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Summary and Conclusion

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Coronary atherosclerosis remains one of the leading causes of morbidity and mortality in the modern western world. It has been established that the majority of acute coronary events (>70%) are caused by plaque rupture followed by thrombus formation. The most common substrate for thrombus formation has been proposed to be the thin cap fibroatheroma; a plaque with a large necrotic core and thin fibrous cap (<65 μm thick) infiltrated by macrophages and lymphocytes. Notably, a considerable number of patients who present with an acute coronary event due to rupture or erosion of an atherosclerotic plaque do not experience any prior symptoms. This observation emphasizes the need to improve the early detection of atherosclerosis. Traditionally, imaging of the coronary arteries has focused on the assessment of the coronary lumen and the presence of severe stenosis by means of invasive coronary angiography. However, invasive coronary angiography only allows the assessment of the lumen and is less suited to evaluate the presence of non-obstructive atherosclerosis, including the presence of (potentially high-risk) plaques. As a result, there is an emerging need for imaging modalities that can identify atherosclerotic lesions with high-risk features indicating increased vulnerability. In this regard, non-invasive techniques may be valuable, as they may identify high-risk patients at a relatively early stage before an adverse events occurs and may provide the opportunity for novel treatment strategies. Accordingly, this thesis focuses on the performance and clinical impact of imaging modalities for the evaluation of atherosclerosis and detection of vulnerable plaques in the coronary arteries.

The general introduction in **Chapter 1** of this thesis provides a description of the rationale to improve early detection of atherosclerosis and vulnerable plaque before the occurrence of an adverse cardiac event. An overview of the currently available invasive and non-invasive modalities for the imaging of coronary atherosclerosis and vulnerable plaque is provided, describing the individual strengths and accuracies of each imaging modality. Lastly, the outline of the current thesis is presented.

Part 1

Part 1 describes the current advances of computed tomography angiography (CTA) in the characterization of coronary atherosclerosis and vulnerable plaque. CTA is a rapidly evolving imaging tool that allows for the non-invasive visualization of coronary atherosclerosis. The temporal and spatial resolution have improved with each new scanner generation, resulting in superior image quality and diagnostic accuracy for the detection of coronary stenosis. CTA is not only able to identify stenosis, but also has the potential to provide information on lesion morphology and plaque composition. Further improvement in plaque characterization, however, is needed before accurate evaluation of plaque composition and subsequent identification of patients at higher risk of events can be achieved.

In **Chapter 2**, the performance of the novel volumetric CTA system regarding plaque characterization was evaluated. This scanner is equipped with 320-detector rows and can potentially improve the ability and reliability of CTA to characterize plaque composition

in the coronary arteries. In this chapter, plaque observations on 320-row CTA were compared to plaque composition on virtual histology intravascular ultrasound (VH IVUS) in 65 patients. On CTA, three plaque types were identified: non-calcified, mixed and calcified. On VH IVUS, plaque composition (% fibrotic, fibro-fatty, necrotic core, dense calcium) and presence of thin cap fibroatheroma (more high risk) were evaluated. Plaque observations on 320-row CTA show good agreement to relative plaque composition on VH IVUS. Moreover, mixed plaques on 320-row CTA parallel the more vulnerable plaque on VH IVUS.

In **Chapter 3**, the relation between plaque composition and degree of stenosis was evaluated by CTA and VH IVUS. In 78 patients CTA was performed (identifying 3 plaque types; non-calcified, calcified, mixed) followed by invasive coronary angiography and VH IVUS. VH IVUS evaluated plaque composition (% fibrotic, fibro-fatty, necrotic core, dense calcium) and plaques were visually classified. For each plaque, degree of stenosis was evaluated by quantitative coronary angiography. Interestingly, plaque types on CTA were equally distributed among significant (≥ 50%) and non-significant stenoses. In addition, VH IVUS observed no differences in % fibrotic, fibro-fatty, dense calcium and necrotic core. Importantly, thin cap fibroatheroma (the more vulnerable plaque) was distributed equally between significant and non-significant stenosis (p=0.18). This study indicates that there is no evident relation between the degree of stenosis and plaque composition or vulnerability.

Chapter 4 assessed the difference in location between site of greatest vulnerability and site of most severe narrowing with invasive VH IVUS. In 92 patients, the site of greatest vulnerability on VH IVUS was defined as the cross-section with the largest necrotic core area per vessel, the maximum necrotic core site and the site of most severe narrowing was defined the minimum lumen area site. The distance from both the maximum necrotic core site and minimum lumen area site to the origin of the coronary artery was evaluated with a dedicated software tool in the longitudinal IVUS view. In addition, the presence of a thin cap fibroatheroma was assessed. Interestingly, there was a substantial difference between the minimum lumen area site and maximum necrotic core site (10.8 ±20.6 mm). Moreover, the maximum necrotic core site was located at the minimum lumen area site in only 7 vessels (5%). In 92 vessels (66%) the maximum necrotic core site was located proximally to the minimum lumen area site and in 40 vessels (29%) distally to the minimum lumen area site. The present findings demonstrate that the site of greatest vulnerability is rarely at the site of most severe narrowing. Moreover, the site of greatest vulnerability is frequently located proximal from the site of most severe narrowing.

In **Chapter 5**, the aim of the study was to systematically investigate the accuracy of CTA for detecting significant stenosis (using conventional coronary angiography as the reference standard) versus detecting the presence of atherosclerosis (using IVUS as reference of standard). CTA correctly ruled out significant stenosis in 53 of 53 (100%) patients. However, 9 patients (19%) were incorrectly diagnosed as having significant lesions on CTA resulting in sensitivity, specificity, positive and negative predictive values of 100%, 85%, 81% and 100%. Interestingly, CTA correctly ruled out the presence of atherosclerosis in 7 patients (100%) and correctly identified the presence of atherosclerosis in 93 patients

(100%). No patients were incorrectly classified, resulting in sensitivity, specificity, positive and negative predictive values of 100%. These findings confirm that the diagnostic performance of CTA is superior in the evaluation of presence or absence of clinically relevant atherosclerosis as compared to the evaluation of significant stenosis.

More accurate lesion assessment may be feasible with CTA as compared to invasive coronary angiography. Accordingly, lesion length assessment was compared between invasive coronary angiography and CTA in patients referred for CTA who underwent subsequent percutaneous coronary intervention in **Chapter 6.** In 89 patients, lesion length was measured from the proximal to the distal shoulder of the plaque on CTA. Quantitative coronary angiography was performed to analyze lesion length. Interestingly, lesion length on CTA was significantly longer than on quantitative coronary angiography (difference 8.8 ±6.7mm, $p<0.001$). Moreover, lesion length visualized on CTA was also significantly longer than mean stent length (CTA lesion length-stent length was 4.2 ±8.7 mm, $p<0.001$). The study concludes that CTA provides more accurate lesion length assessment than invasive coronary angiography and may facilitate improved guidance of percutaneous treatment of coronary lesions.

Several previous studies have identified specific plaque characteristics which are frequently observed with CTA in patients presenting with acute coronary syndrome. Among these characteristics, a spotty pattern of calcifications and positive remodeling have been related to the presence of acute coronary syndrome. **Chapter 7** systematically compared calcification patterns in plaques visualized on CTA with vulnerable plaque characteristics on VH IVUS in 108 patients. Interestingly, plaques with small spotty calcifications on CTA were related to more vulnerable plaque characteristics on VH IVUS. **Chapter 8** further addressed this issue by assessing the association between positive remodeling on quantitative CTA and vulnerable plaque characteristics on VH IVUS. On CTA, the remodeling index was determined for each lesion using a novel dedicated quantitative analysis strategy. Notably, the study confirms that lesions with positive remodeling on CTA were associated with a higher percentage necrotic core and a higher prevalence of thin cap fibroatheroma. Accordingly, evaluation of spotty calcifications and remodeling on CTA may be valuable markers for plaque vulnerability.

Part 2

In part 2 of this thesis, the relation between characterization of atherosclerosis on CTA and the effect on clinical management was evaluated in more detail. **Chapter 9** provides an overview regarding the evolving role of coronary CTA (including coronary calcium scoring) in the diagnosis of patients with acute chest pain which constitute a common and important diagnostic challenge. As a result of rapid developments in coronary CTA technology, high diagnostic accuracies for detecting coronary stenosis are obtained. Additionally, CTA is an excellent modality in patients whose symptoms suggest other non-coronary causes of acute chest pain such as aortic aneurysms, aortic dissection, or pulmonary embolism. However, although CT shows great potential in evaluating patients

with acute chest pain, more randomized clinical trials are needed to determine the value of this technique in this challenging patient population.

Chapter 10 addresses effective strategies to reduce radiation dose with CTA. On the one hand, a conservative approach regarding radiation dose may result in a high level of image noise and therefore in non-diagnostic images. On the other hand, higher radiation exposure may put patients at unnecessary risk of radiation damage. Thus, effective strategies to reduce radiation dose, such as prospective triggering, heart rate control, ECG-modulation of the tube current, and use of tube voltage below 100 kV, will need to be applied in the clinical setting.

Chapter 11 evaluated the diagnostic accuracy of the novel 320-row CTA in the evaluation of significant coronary artery stenosis in 64 patients, compared with invasive coronary angiography as the standard of reference. High sensitivity, specificity, and positive and negative predictive values to detect ≥ 50% luminal narrowing on a patient basis of 100%, 88%, 92%, and 100%, respectively, were demonstrated. The study concludes that 320-row CTA allows for accurate non-invasive assessment of significant coronary artery disease (CAD). **Chapter 12** further addressed the diagnostic accuracy of 320-row CTA, specifically in patients presenting with acute chest pain and examined the relation to outcome during follow-up. Among the 106 patients presenting with chest pain, 22% had a normal CTA, 18% had non-significant CAD on CTA and 55% had significant CAD on CTA (5% had uninterpretable CTA). Sensitivity, specificity, and positive and negative predictive values to detect significant CAD on CTA were 100%, 87%, 93%, and 100%, respectively. The study concludes that in patients presenting with acute chest pain, an excellent clinical performance for the non-invasive assessment of significant CAD is demonstrated using 320-row CTA. Importantly, normal or non-significant CAD on CTA predicted a low rate of adverse cardiovascular events and favorable outcome during follow-up.

The aim of **Chapter 13** was to evaluate the relationship between the calcium score and the degree and character of atherosclerosis in patients suspected of acute coronary syndrome versus patients with stable CAD. Overall, 112 patients were studied; 53 with acute coronary syndrome and 59 with stable CAD. CTA and VH IVUS were performed to evaluate plaque characteristics. Interestingly, if the calcium score was zero, patients with acute coronary syndrome had a higher mean number of plaques and non-calcified plaques on CTA than patients with stable CAD. In zero calcium score, VH IVUS demonstrated that patients with acute coronary syndrome had a larger amount of necrotic core area and higher mean number of thin cap fibroatheroma than stable CAD. Thus, even in the presence of a zero calcium score, patients with acute coronary syndrome have increased plaque burden as well as increased vulnerability as compared to stable CAD.

The aim of **Chapter 14** was to determine the relation between CTA findings and the rate of subsequent invasive coronary angiography and revascularization. A total of 1042 CTA investigations were available for analysis. In patients with significant CAD on CTA, subsequent invasive coronary angiography rate was 64%. In patients with non-significant CAD on CTA, subsequent invasive coronary angiography rate was 12% and in patients with normal CTA results, subsequent invasive coronary angiography rate was 3.6% ($p<0.001$).

Of patients with significant CAD on CTA, revascularization rate was 36%, as compared to a revascularization rate of 0.3% in patients with non-significant CAD on CTA and no revascularizations in patients with a normal CTA results ($p<0.001$). This chapter concludes that CTA results are strong and independent determinants of subsequent invasive coronary angiography and revascularization.

Previous studies have shown that the presence of stenosis alone on CTA only has a limited value for predicting the presence of ischemia on myocardial perfusion imaging. In the last chapter (**Chapter 15**), different variables of atherosclerosis on CTA were related to ischemia on myocardial perfusion imaging to determine the different predictors of ischemia in 514 patients. On a patient basis, multivariate analysis showed that the degree of stenosis (presence of ≥70% stenosis, OR 3.5), plaque extent and composition (mixed plaques ≥3, OR 1.7 and calcified plaques ≥3, OR 2.0) and location (atherosclerotic disease in left main coronary artery and/or proximal left anterior descending coronary artery, OR 1.6) were independent predictors for ischemia on myocardial perfusion imaging. In addition, CTA variables of atherosclerosis such as plaque extent, composition and location had significant incremental value for the prediction of ischemia over the presence of ≥70% stenosis. Thus, in addition to the degree of stenosis, CTA variables of atherosclerosis describing plaque extent, composition and location are predictive of the presence of ischemia on myocardial perfusion imaging.

Conclusions

During the past few years CTA has rapidly developed into a versatile non-invasive imaging modality. While imaging of the coronary arteries to determine or rule out the presence of stenosis will remain one of the main indications, additional information on plaque severity and composition can be obtained. The improvements in technology (faster gantry rotation times, an increasing number of detectors, volumetric image acquisition) and consequential improvement in image quality have resulted in advances in the characterization of coronary atherosclerosis and vulnerable plaque. Interestingly, the diagnostic performance of CTA was superior in the evaluation of presence or absence of clinically relevant atherosclerosis as compared to the evaluation of significant stenosis. Regarding plaque observations with the novel 320-row CTA scanner, the results showed good agreement to relative plaque composition on invasive VH IVUS. Moreover, mixed plaques on 320-row CTA paralleled the more vulnerable plaque on VH IVUS. In addition, lesions with spotty calcifications and positive remodeling on CTA were associated with a higher percentage necrotic core and a higher prevalence of vulnerable plaques. Accordingly, evaluation of spotty calcifications and remodeling on CTA may be valuable markers for plaque vulnerability.

The relation between characterization of atherosclerosis on CTA and its effect on clinical management was also evaluated. As a result of rapid developments in coronary CTA technology, high diagnostic accuracies of 320-row CTA for detecting coronary stenosis were obtained in patients with stable chest pain complaints as well as in patients presenting with acute chest pain. In addition, although a zero calcium score has important

prognostic value, patients with acute coronary syndrome and zero calcium had increased plaque burden as well as increased vulnerability as compared to patients with stable chest pain. Accordingly, absence of coronary calcification did not exclude the presence of clinically relevant and potentially vulnerable atherosclerotic plaque burden in patients with acute coronary syndrome. Lastly, in addition to the degree of stenosis, CTA variables of atherosclerosis describing plaque extent, composition and location were predictive of the presence of ischemia on myocardial perfusion imaging. Possibly, these results may allow a more refined and individualized assessment of patients undergoing CTA imaging and provide the basis for the development of an algorithm to improve identification of patients requiring more aggressive therapy or intervention.