Coronary heart disease on coronary computed tomography angiography: in search of the vulnerable patient

Rosendael, S.E. van

CHAPTER 6

Summary, Conclusions and Future Perspectives

Summary

This thesis investigated how CCTA, a non-invasive imaging technique, may be used in clinical practice to better characterize coronary heart disease and to improve risk-stratification. CCTA is an imaging technique for the evaluation of coronary artery disease throughout the entirety of disease severity and enhances information regarding plaque extent, plaque composition, and PCAT surrounding the arteries.

In Chapter 2 of this thesis, CCTA was used to assess PCAT attenuation values in patients with no atherosclerosis on CCTA. A total of 109 individuals were included and the proximal parts of 320 coronary arteries were evaluated. PCAT was defined and calculated as the average attenuation of all voxels between -30 and -190 Hounsfield units (HU) and sampled within a radial distance from the outer vessel wall equal to the vessel diameter. There was a significant difference in mean PCAT attenuation between the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA), with lower values in the LAD compared to the LCx and RCA (LAD: -67.8 ± 7.8 HU vs. LCx: -62.6 ± 6.8 HU vs. RCA: -63.6±7.9 HU, p<0.001). Furthermore, sex differences were observed in all three coronary arteries with significantly higher PCAT attenuation values in men compared to women. These results underscore the importance of analyzing all three vessels and the need to adjust for sex when analyzing PCAT. In addition, our PCAT attenuation values were relatively higher compared to previous studies. PCAT attenuation has been shown to be significantly associated with technical as well as patient characteristics, and these factors need to be taken into account when analyzing PCAT.[1-3] With regard to technical factors, significant differences in mean PCAT attenuation are demonstrated based on the model of the CT scanner used. Further, pixel spacing and tube voltage and current were also significantly associated with differences in PCAT attenuation as well as the heart rate of the patient.

In Chapter 3, serial CCTA scans of 649 patients have been evaluated to assess factors associated with statin non-response, defined as an absolute increase of 1.0% or more percent atheroma volume per year, despite the use of statins. Statin non-response was present in 205 (31.5%) patients, and factors independently associated were diabetes, the number of high-risk plaque features, noncalcified and calcified percent atheroma volume (OR:1.41 (0.95-2.11), OR:1.15 (1.09-1.21), OR:1.06 (1.02-1.10), OR:1.07 (1.03-1.12), respectively). When an additional requirement was added and statin non-response was defined as >1.0% increase of percent atheroma volume per year and progression of fibro-fatty plaque or low-attenuation plaque (N=125, 19.2%) only the number of high-risk plaque features and non-calcified percent atheroma volume at baseline were independent associates (OR: 1.21 (1.06-1.21) and OR: 1.08 (1.03-1.13), respectively). These results suggest that patients with high-risk plaques and with the largest plaque burden at baseline represent the highest risk for statin non-response. Given the association of plaque progression with major adverse cardiovascular events, additional risk-reducing therapies might be necessary in these patients.

In Chapter 4 the Leiden CCTA risk score was assessed in 24,950 patients to translate the patient's totality of plaque in the coronaries into a single score and to investigate age- and sex-related differences. The score (range 0 to 42) incorporates plaque extent, severity, location and composition, with higher weights for more proximal disease, higher stenosis severity, and more noncalcified or mixed plaque composition. The score was stratified into 3 groups: 0-5, 6-20 and >20, as these values were previously shown to discriminate adverse events best.[4] The risk score increased with age for both sexes, however the age where the median risk score was above 0 was between 52 and 56 for men and between 64 and 68 for women (p<0.001). This sex difference became smaller with increasing age, but the score remained significantly higher for men in every age group. Cox-regression analysis adjusted for confounders age and cardiovascular risk factors showed an independent association between the CCTA risk score and major adverse cardiovascular events (Leiden CCTA risk score 6-20: HR 2.29 [1.69-3.10]; Leiden CCTA risk score >20: HR 6.71 [4.36-10.32] in women, and Leiden CCTA risk score 6-20: HR 1.64 [1.29-2.08]; Leiden CCTA risk score >20: HR 2.38 [1.73-3.29] in men) with for women higher magnitudes of risk. For pre-and post-menopausal analyses, the cohort was dichotomized into pre- and postmenopausal groups based on age. These analyses showed comparable adjusted hazard ratios between premenopausal women and men (<55 years). Post-menopausal analyses showed higher prognostic values for women, especially in the group with the highest Leiden CCTA risk score (Leiden CCTA risk score 6-20: HR 2.21 [1.57-3.11]; Leiden CCTA risk score >20: HR 6.11 [3.84-9.70] in women; Leiden CCTA risk score 6-20: HR 1.57 [1.19-2.09]; Leiden CCTA risk score >20: HR 2.25 [1.58-3.22] in men). The increased risk for women within the highest atherosclerotic burden group appears to be driven by post-menopausal women. More intensive preventive medical therapies may be suitable for this group, even in the absence of prior events. Chapter 5 describes the analysis of the coronary vascular volume to left ventricular mass (V/M) ratio obtained by CCTA in 2378 patients. All segmented coronary arteries were summed for the calculation of the total coronary arterial lumen volume. The myocardial volume was extracted from CCTA and multiplied by the specific density of the myocardium (1.05g/ml), resulting in the left ventricle mass. 1346 (56%) patients had hypertension and we hypothesized a lower V/M ratio in these individuals compared to normotensive patients, as hypertension has been associated with reduced coronary vascular reserve.[5-14] However, after adjustment both coronary volume and ventricular mass were higher in hypertensive patients (Least square mean difference estimate: 196.3 (95% CI: 119.9, 272.7)mm^3, p<0.001, and Least square mean difference estimate: 5.60 (95% CI: 3.42, 7.78) g, p<0.001, respectively) whereas the V/M ratio was not significantly different between both groups (Least square mean difference estimate: 0.48 (95% CI: -0.12, 1.08) mm^3/g, p=0.116). These findings suggest that in our cohort, the reduced coronary vascular reserve in hypertensive patients is not caused by an abnormal coronary flow reserve.

Conclusions and Future Perspectives

CCTA has developed into a reliable, noninvasive imaging technique with high accuracy for the detection and exclusion of coronary artery disease. A scan without atherosclerosis in the coronaries excludes plaque as the cause of the cardiac symptoms and predicts a long-term low risk for cardiovascular events. Advances in CT technologies allow detailed atherosclerotic assessment with plaque quantification and assessment of PCAT surrounding the arteries.[15]

PCAT attenuation has been postulated as a novel biomarker to detect coronary inflammation earlier and in this thesis we attempted to establish reference values. It is a relatively new parameter which is influenced by several factors, many studies use different methods of measurement and there is no clear consensus on the gold standard. More research is needed to better understand the association of PCAT with atherogenesis and events, and how it can best be implemented clinically.

Changes in plaque over time can be identified by serial CCTA scans and plaque progression is associated with worse outcomes. Statins reduce major cardiovascular events, but residual cardiovascular risk remains. As described in this thesis, the number of high-risk plaque features and baseline plaque burden were the strongest determinants of statin non-response. Whether these patients may be candidates for other cardiovascular risk-reducing pharmaceutical therapies necessitates further research.

The atherosclerotic burden has been comprehensively shown to be a strong prognosticator of events. We measured the atherosclerotic burden with the Leiden CCTA risk score and explored sex differences between the onset of atherosclerosis. This thesis identified differences in magnitudes of risk between sexes. There is an approximate 12-year delay in the onset of atherosclerosis for women, however women with extensive atherosclerosis, are at significantly higher risk for MACE than men, mainly driven by the post-menopausal cohort. Age and sex could be considered as extra parameters to be integrated into such scores. Further, more strict thresholds in scores for women and more intensive medical therapies may also be needed in these patients.

The V/M ratio was after correcting for potential confounders preserved in patients with hypertension compared to patients without hypertension. These findings do not support the hypothesis, that the abnormal perfusion reserve would be caused by a reduced V/M ratio, however we cannot exclude this as a possibility in different cohorts, and this needs further investigation.

Last, photon-counting CT, a new promising technique with improved spatial resolution is expected to substantially improve cardiovascular imaging. Artifacts such as blooming which results in overestimation of stenosis will be reduced. Improved visualization and evaluation of intraluminal stents and high-risk plaque features can be expected as well.[16]

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