Advancements in cardiovascular imaging: serial coronary CT and myocardial CT perfusion quantification techniques

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1 General introduction

Coronary computed tomography angiography (CCTA) is a widely used non-invasive imaging modality in the diagnosis of coronary artery disease (CAD), allowing for both quantitative and qualitative plaque assessment (1). It fulfils a very important role in the early diagnosis of CAD which still remains one of the leading causes of mortality and loss of disability-adjusted life years worldwide (2). In recent years use of serial CCTA has emerged in which baseline and follow-up CCTA scans can be compared thus allowing for the assessment of changes in plaque burden and plaque morphology (3, 4). Serial CCTA has not only demonstrated its value in the assessment of plaque progression or regression but also in the assessment of changes in epicardial adipose tissue (EAT) in which relatively larger volumes of EAT are associated with rapid and early plaque progression (5). However, as mentioned earlier CCTA is primarily capable of quantitative and qualitative plaque assessment. Yet, the assessment of ischemic myocardium using CT myocardial perfusion (CTP) could allow for functional assessment of CAD, the latter is of importance for prognosis assessment and in the decision to revascularize patients (6, 7).

CCTA and MRI both offer advantages in the assessment of left ventricular (LV) mass and wall thickness but MRI remains the gold standard (8, 9). However, recent technological advancements in CCTA such as improved spatial resolution have enabled its application beyond coronary assessment allowing for the assessment of LV mass and wall thickness (8). This is particularly important as this may offer a resolution for patient with contraindications to MRI, such as those with cardiac implanted devices or severe claustrophobia (10).

The introduction of machine learning algorithms may further refine these imaging techniques for the assessment of LV dimensions.

This thesis focuses on the development and validation of novel CT-based methods for quantifying ischemia, quantifying plaque changes on serial CCTA and quantification of LV mass and wall thickness as opposed to the gold standard MRI. By expanding the methodological capabilities of CCTA, this research aims to support the broader application of this imaging modality in comprehensive cardiac assessment.

Role of serial coronary artery CT in the evaluation of coronary artery disease

Serial CCTA allows for a non-invasive assessment of changes in plaque burden (Figure 1) and plaque morphology as well as changes in EAT (3-5). EAT is associated with CAD development as it has been shown to share the same embryologic origin as intra-abdominal fat which in turn is associated with CAD development (11). Multiple studies using serial CCTA have shown that baseline quantitative plaque characteristics, along

with measurable changes in plaque volume, are more predictive of plaque progression and major adverse cardiac events (MACE) over time than qualitative plaque features (4, 12-14). This underlies the importance of accurate identification and risk stratification of patients at risk for future atherosclerosis progression and MACE.

Several studies have shown that serial CCTA is a viable method for evaluating plaque changes (4, 13). Nevertheless, the process of co-registering coronary vessels and analyzing plaque changes between baseline and follow-up scans continues to rely on manual techniques using anatomical landmarks (15-17). Ideally an automatic co-registration of coronary vessels would be used as has recently been developed by Cao et al(18). Yet, cut-off values for plaque progression and or regression remain to be identified. A technique for objectively evaluating plaque dynamics on CCTA involves the use of patient-specific thresholds as is demonstrated in this thesis. These thresholds are derived from calibration graphs generated using two-phase scan sets, where differences in negative and positive plaque thickness are plotted against the scan quality, measured as the contrast to noise ratio (CNR). This allows for the assessment of plaque progression using patient specific and vessel specific thresholds based on scan quality.

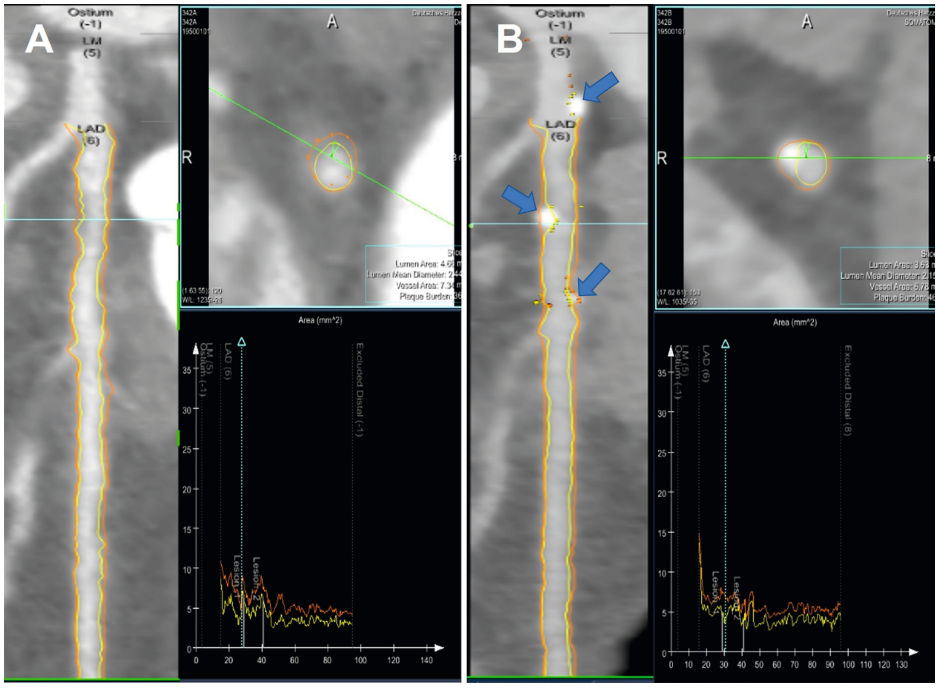

Figure 1. Example adapted from Weber et al (3). of a patient who has undergone serial CCTA in which the baseline scan is shown in panel A and the follow-up scan in panel B. A total of three newly formed calcified plaques are seen in the follow-up scan as marked by the blue arrows.

Myocardial cardiac CT perfusion and quantification

As mentioned before, CCTA is a valuable non-invasive imaging modality in CAD assessment. However, its main role involves assessment of stenosis severity. Additional CTP allows for the evaluation of ischemic myocardium which is important for prognosis and plays a key role in determining whether patients should undergo revascularization. This decision is influenced by the degree of hypoperfusion (ischemia) in the myocardium relative to the mass of myocardial tissue distal to the coronary stenosis (1, 6, 7). However, nowadays CTP is still assessed routinely by visual analysis in a semi quantitative manner. Full quantification of myocardial ischemia is discussed in this thesis using the Voronoi algorithm.

The Voronoi algorithm is a mathematical method used to partition a two-dimensional plane or three-dimensional space into regions based on the shortest distance to predefined points. Applying this algorithm to myocardial tissue allows for segmentation of the myocardium according to the supplied territory of each coronary vessel (19). Subsequently, areas of ischemia on CTP can be correlated to the corresponding area perfused by each of the coronary arteries. In the case of a severe stenosis this also allows for the correlation of the "subtended mass" to the subsequent area of ischemia. In which the subtended mass is defined as the mass of myocardial tissue supplied by a coronary artery distally from the stenosis (Figure 2).

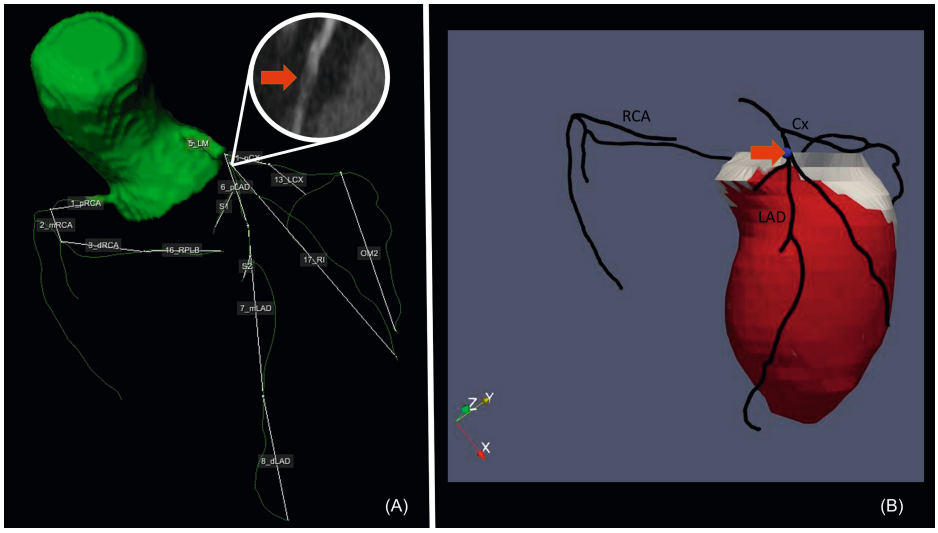

Figure 2. Example of a patient with a stenosis in the proximal left anterior descending artery (LAD) as marked by the red arrow in panel A and B. The red area in panel B represents the "subtended mass" calculated using the Voronoi algorithm.

MRI is still considered the gold standard in the assessment of LV mass and wall thickness (9). However, the high diagnostic accuracy of CCTA for the detection of CAD have made it a widely used imaging modality over the past few years (20). The role of CCTA as a tool for LV mass and LV wall thickness is less explored but would be especially beneficial for patients with contraindications for MRI (8, 10). LV dimension assessment is especially important as both LV hypertrophy and increased LV wall thickness are independent risk factors for cardiovascular morbidity and mortality, regardless of the underlying cause (21). Nowadays, advancements in artificial intelligence have opened the door for its use in LV contour placement, a crucial step of LV dimension quantification. Using AI driven algorithms for LV contour placement on both CCTA and MRI – as opposed to manual contour placement - has been regarded as a time saver (22, 23). Its applicability in the comparison of LV mass and LV wall thickness on CCTA versus MRI is explored in this thesis.

Thesis outline

Part 1 of the thesis describes the role of serial CCTA scanning in the evaluation of coronary artery disease and demonstrates a novel method for visualization of plaque differences applied to serial CCTA. **Chapter 2** presents a comprehensive review of literature on how serial CCTA may be used for the assessment of both quantitative and qualitative plaque features as predictors of plaque progression and MACE. **Chapter 3** describes a novel method for the quantification of local plaque thickness differences on CCTA using scan-quality-based-vessel-specific thresholds for the assessment of coronary plaque progression and or regression. **Part 2** focusses on methods that allow for quantification of myocardial ischemia using CTP as well as quantification of LV dimensions using artificial intelligence (AI) for contour placement. **Chapter 4** describes the relationship between quantified myocardial ischemia as assessed by CTP and the myocardial area at risk, defined as the myocardial area distal from a 50% or 70% coronary stenosis. **Chapter 5** outlines the correlation of the quantified ischemia on CTP and the myocardial area at risk. **Chapter 6** analyses the assessment of LV mass and wall thickness on CT by comparing LV mass and wall thickness measured on CT versus the gold standard of MRI using machine learning algorithms for LV contour placement.

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