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

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7 Summary, conclusions and future perspectives

Summary

Chapter1 includes the general introduction and thesis outline. CCTA in combination with CTP allows for quantitative, qualitative and functional assessment of CAD. Furthermore, quantification of myocardial ischemia on CTP and using a Voronoi algorithm for myocardial segmentation allows for quantitative correlation of myocardial ischemia to the corresponding coronary stenosis which is vital for revascularization. Following the widespread use of CCTA use of serial CCTA has emerged in recent years allowing for the assessment of changes in plaque burden and plaque morphology. Technological advancements have enabled the use of automatic alignment in the comparison of baseline and follow-up scans whilst also allowing for quantitative assessment of plaque changes. Specific advancements in CCTA image quality have enabled CCTA to be used for LV dimension assessment, a task still mainly performed by cardiac MRI. **Chapter 2** consists of a review article exploring the use of serial CCTA for predicting plaque progression and MACE. The following topics are described. Quantitative baseline plaque features as well as quantitative plaque changes seem to be more predictive of MACE and/or plaque progression as compared to qualitative plaque features. Furthermore, higher epicardial fat volume (EFV) at baseline was associated with the progression or development of coronary artery plaque. Serial CCTA has also been proven useful in the assessment of statin therapy efficacy on plaque progression as it has been revealed that statins slowed the overall progression of coronary atherosclerosis volume and induced an increase in plaque calcification and reduction of high risk plaque features. Certain challenges remain with regard to the clinical use of serial CCTA. For instance, different scanners may be used at baseline and follow-up scans leading to a variability in plaque volume assessment. This highlights the importance of using standardized acquisition protocols for both baseline and follow-up CT scans. Furthermore, no expert consensus is available on the ideal inter-scan interval between baseline and follow-up CT scans but based on recent studies this interval could potentially be set at 1-2 years. **Chapter 3** describes the development of patient specific thresholds for determining plaque progression and/or regression on serial CCTA. Delineation of coronary vessel and lumen contours is necessary for plaque quantification which is vital for CAD assessment on both CCTA and serial CCTA. This delineation process is dependent on scan quality which can be quantified using the contrast to noise ratio (CNR). Consequently, thresholds are necessary to differentiate actual changes in plaque thickness from changes caused by inaccuracies in vessel and lumen wall delineation. A cohort of 50 patients with available CCTA was used in which two different phases from each scan were used for the delineation of 300 coronary vessels and CNR calculation for each vessel. The average CNR value was 13.4 ± 3.6. The average positive and negative differences in measured plaque thickness were 0.7 ± 0.3 and -0.9 ± 0.6 mm, respectively. The inter-observer correlation for CNR values was excellent, with a correlation coefficient of 0.872 ($p < 0.001$). Found plaque differences among these two phase scan sets may be attributed to inaccuracies in plaque delineation as plaque differences between two reconstructed phases from the

same scan from the same patient should always be zero. Subsequently, largest positive and negative plaque differences were plotted against the vessel-specific CNR. Plots revealed a small trend in which larger plaque differences corresponded with a lower CNR. By using linear regression analysis vessel specific and patient specific thresholds could be obtained based on the vessel-specific CNR. **Chapter 4** demonstrates the possibility of full quantification of myocardial perfusion defects as assessed by CTP. Nowadays assessment of CTP is done semi quantitatively by visual analysis. Full quantification of myocardial perfusion defects and subtended myocardial mass seems feasible as it allows for identifying the distribution of myocardial ischemia over the coronary artery lesion(s). Thirty-three patients with a combined CCTA and CTP protocol with good or excellent imaging quality on CTP were analyzed using the Voronoi algorithm. This algorithm allows for dividing tissue in different segments according to which blood vessel is closest to the segment. A total of 64 relevant coronary artery lesions were assessed. Average values for total subtended mass, subtended mass per lesion, perfusion defect mass and perfusion defect mass per lesion were 69, 36, 7 and 3 grams respectively. In 19/33 patients (58%) the total perfusion defect mass could be distributed over the relevant coronary artery lesion(s). **Chapter 5** explores the correlation between the quantified myocardial area at risk and quantified areas of myocardial ischemia. Forty-two patients with a combined CCTA and CTP protocol and at least one stenosis of ≥ 50% on CCTA were selected for analysis. The myocardial area at risk was calculated using a Voronoi-based segmentation algorithm on CCTA and was defined as the sum of all territories related to a ≥ 50% stenosis as a percentage of the total LV mass. The ischemic burden was calculated as the quantified area of myocardial ischemia as a percentage of the total LV mass. LV contours were automatically placed using a machine learning algorithm. A total of 77 coronary lesions with a luminal stenosis of ≥ 50% were assessed. Analysis was done separately for stenosis of ≥ 50% and ≥ 70%. Average myocardial area at risk for stenosis ≥ 50% and ≥ 70% were 59% and 37%, respectively. Average ischemic burden for stenosis ≥ 50% and ≥ 70% were 23% and 24%, respectively. There was a moderate correlation of the ischemic burden versus myocardial area at risk for stenosis of ≥ 50% ($r = 0.564$; $p < 0.01$). A good correlation was found for the ischemic burden versus the area at risk for stenosis of ≥ 70% ($r = 0.708$; $p < 0.01$). **Chapter 6** assesses the use of CCTA for LV mass and wall thickness assessment as compared to the gold standard of cardiac MRI. Fifty-seven patients with available CCTA and MRI with an interscan interval of 6 months maximum were analyzed. Average LV mass and wall thickness for CCTA and cardiac MRI were 127 grams, 128 grams, 7mm and 8 mm, respectively. Bland–Altman plots demonstrated mean differences and corresponding 95% limits of agreement of –1.26 (25.06; –27.58) and –0.57 (1.78; –2.92), for LV mass and average LV wall thickness, respectively. Mean differences and corresponding 95% limits of agreement for wall thickness per region were –0.75 (1.34; –2.83), –0.58 (2.14; –3.30), and –0.29 (3.21; –3.79) for the basal, mid, and apical regions, respectively. Ultimately, use of CCTA for LV dimension assessment is feasible and shows good agreement with cardiac MRI.

General discussion

This thesis explores the evolving role of CCTA in cardiovascular imaging. Hereby focusing on the utilization of serial CCTA on plaque progression and/or regression, quantifying myocardial ischemia on CTP and subsequently correlating this to the myocardial area at risk and lastly using CCTA as an imaging tool for LV morphology evaluation.

Across five original studies, the results support the increasing clinical value of CCTA as a multipurpose imaging tool for both anatomical and functional assessment, especially when aided by advanced computational methods.

A proposed method for the objective assessment of plaque dynamics using patient-specific thresholds on CCTA allows for the direct visualization and quantification of plaque thickness differences, and shows good visual agreement with the plaque localization. Absence of a gold standard may be regarded as a severe limitation however Cao et al demonstrated excellent correspondence using artificially created plaque changes (1).

Adequate detection of plaque changes is highly important as multiple studies have demonstrated that especially quantitative plaque features (contrary to qualitative features) are predictive of plaque progression and MACE (2-5). Furthermore, the capability of subclinical atherosclerosis progression and/or regression detection may be especially beneficial for timely treatment in order to prevent atherosclerosis progression (6).

In two additional studies the utility of CCTA was expanded to the functional domain in terms of ischemia detection using CTP. Primarily it was demonstrated that ischemia may be quantified and subsequently correlated with the subtended mass as is determined by the coronary stenosis. These studies hereby confirmed that CCTA combined with adenosine stress protocols such as CTP can provide insight into myocardial ischemia and its relation to relevant CAD localization. This reinforces the emerging notion that CCTA aided by a adenosine stress protocol could perhaps replace or complement other myocardial perfusion techniques such as PET or SPECT in specific patient cohorts (7).

Lastly, an evaluation was made using CCTA for quantifying left ventricular mass and wall thickness and compared with the gold standard of cardiac MRI using AI-driven segmentation showing excellent agreement. An alternative to MRI is especially important as patient may have insurmountable contraindications such as cardiac devices or claustrophobia (8). This further supports the idea of CCTA as a single modality capable of assessing coronary arteries, myocardial perfusion - by means of adding an adenosine stress protocol - and cardiac morphology.

What strengthens this thesis is the focus on automation -for example by leveraging AI algorithms- and consistent use of advanced image analysis techniques such as applying a Voronoi algorithm for myocardial segmentation.

However, there are also limitations. All studies were retrospective in nature and based om relatively small single-center cohorts, limiting generalizability. Although the review article on the utilization of serial CCTA for the assessment of plaque progression and/or regression included clinical endpoints none of the other studies include this feature. This prevents definitive conclusions about the prognostic implications of the derived metrics. However we do feel this is inherent to research focusing on the development of new technological methods for (aided) image analysis as is the case in this thesis. Furthermore, while AI tools improve efficiency, they can lack transparency, raising questions about model robustness across diverse datasets (9).

Conclusion and future perspectives

CCTA has become a widely used imaging modality for the detection of coronary artery stenosis with a high degree of diagnostic accuracy (10). As such, serial CCTA has become available in the assessment of plaque progression and or regression. Furthermore, it allows for studying the relationship of both quantitative and qualitative plaque features with regard to the prediction of plaque progression and MACE over time (11, 12). Following, the results of a review paper included in chapter 2 of this thesis is has been shown that not primarily qualitative plaque features but quantitative plaque features have the biggest impact on plaque progression and MACE. This underlies the potential importance for serial CCTA which is yet to be introduced in regular risk stratification of patients. With regard to further implementation of serial CCTA chapter 3 of this thesis describes the use of automatic co-registration of baseline and follow-up scans as well as development of patient specific cut-off values for determining plaque progression or regression for optimal usage of serial CCTA (1).

Addition of CTP to CCTA is beneficial as it allows for functional assessment of coronary artery stenosis which is crucial in the decision to revascularize patients (13). Nowadays, assessment of CTP is still done semi-quantitatively by visual analysis. In chapter 4 and 5 of this thesis it has been demonstrated that fully quantifying perfusion defects is possible and allows for quantitative correlation of hemodynamically significant lesions to areas of myocardial hypoperfusion. Furthermore, this allows for correlation of the "subtended mass"—the myocardial mass distal to a stenosis—with the area of myocardial hypoperfusion, demonstrating a good relationship with increasing stenosis degree.

The use of CCTA has been primarily focussed on coronary artery stenosis assessment yet with regard to its increasing spatial resolution other potential uses arise such as LV

dimension assessment (14). To this day cardiac MRI remains the gold standard when it comes to LV dimension assessment (15). Assessment of LV dimensions is crucial as both LV hypertrophy and LV wall thickness are independent risk factors of cardiac death (16). This thesis has demonstrated that CCTA has proven to be a reliable alternative for LV mass and LV wall thickness assessment as compared to MRI. This process may be further optimized by use of machine learning for LV contour placement on both CCTA and MRI allowing for substantial time gain as is pointed out before in several other studies (17, 18).

With the coming age of quantum computing and artificial intelligence it is interesting to see how these processes may be automated further in the (near) future (19).

Recently, use of photon counting CT has emerged and is capable of very high resolution imaging due to its increased spatial and temporal resolution which is essential for the assessment of small structures such as coronary plaques (20). Phantom studies have also demonstrated the feasibility of photon counting CT for the accurate quantification of iodine concentrations across various levels and body sizes, this is especially vital for the potential use of photon counting CT in the assessment of myocardial ischemia (21). Current assessment of iodine maps using standard multidetector CT scanners is often hindered due to beam hardening and other artefacts. As such photon counting CT may prove especially useful by reducing these artefacts along its increased spatial and temporal resolution (22). Furthermore, the ability to count photon numbers and energy enables the reconstruction of multienergy spectral images allowing for material decomposition analysis and thus better characterization of plaques. As such photon counting CT offers numerous potential advantages as compared to current standard multidetector CT scanners and is highly likely to be routinely used in CCTA assessment in the future (23). In this thesis photon counting CT was highlighted due to its direct relevance to CCTA and CTP for atherosclerosis and ischemia assessment as well as use of CCTA for LV morphology analysis, which are central to the studies presented. However, photon counting CT represents just one of several highly anticipated innovations in cardiac imaging. For example, fluripiridaz PET/CT is another notable advancement and has demonstrated superior image quality, higher diagnostic accuracy and lower radiation exposure as compared to traditional SPECT imaging. As such, fluripiridaz PET/CT is particularly advantageous in myocardial perfusion imaging, hereby offering improved detection of coronary artery disease (24).

Henceforth, a combination of easy-to-use tools aided by artificial intelligence and increased image quality will pave the route for new frontiers in cardiovascular imaging.

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