Quantitative cardiac dual source CT; from morphology to function
Assen, van, Marly

DOI: 10.33612/diss.93012859

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date: 2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
General introduction and outline of this thesis
Cardiovascular diseases (CVDs) are a large contributor to the global mortality rate. A total of 17.9 million people die from CVDs every year, which accounts for 31% of all global deaths (1). This is expected to increase in the upcoming years due to the aging population and the increased westernization of third world countries. Non-invasive imaging techniques, such as computed tomography (CT) imaging, have been playing a growing role in the risk assessment, diagnosis, and prognosis of CVDs and especially in coronary artery disease (CAD). Cardiac CT imaging is being increasingly used to visualize CAD along the entire myocardial ischemic cascade from its earliest manifestations of vessel wall abnormalities to its final stages of myocardial infarction (2). This makes CT the only modality with the potential to image all phases of the ischemic cascade within one modality.

One of the first visualizable steps in the ischemic cascade is the development of coronary artery calcification which can be easily visualized using CT, even in asymptomatic patients. Coronary artery calcium scoring (CACS) serves as a reliable tool for CVD risk assessment and to guide follow-up testing (3,4). Traditionally CACS is performed on dedicated ECG-triggered non-contrast cardiac CT acquisitions. However, with the increased use of CACS and the increased numbers of additional CACS acquisition, we also see an emerging role of non-contrast non-gated chest CTs and contrast enhanced ECG-triggered coronary computed tomographic angiography (CCTA) acquisitions for the analysis of coronary calcium. The use of these already clinically accepted acquisitions allows for risk assessment without the need for an additional acquisition, thereby reducing radiation dose. Artificial Intelligence could aid to reduce the variability and decrease the labor intensity of this task. A step further from coronary calcium evaluation is the assessment of coronary plaque. CCTA is an established technique to evaluate plaque morphology and its application in this context has the potential to reduce unnecessary invasive testing and improve outcomes, due to its high negative predictive value and its unique ability to rule out obstructive CAD (5). Studies have shown that the addition of morphological and functional plaque characteristics, such as plaque burden and composition, can aid in the diagnosis and prognostication of CAD patients (6,7). Plaque analysis is currently limited by the use of predetermined thresholds, hindering generalization over different scanners and scan protocols and further hindered by not taking into account differences in contrast intensity and inter-patient variability.

Although CCTA has proven its worth in the last decade, the abundant amount of research done on CCTA has also confirmed that anatomical evaluation alone is suboptimal for the accurate evaluation of CAD (8,9). Hence, this is where the functional evaluation of CAD comes into play. Simultaneous anatomical and functional assessment of CAD is not a new idea but has been around since the emersion of electron beam CT imaging over 30 years ago. However, in recent years the emphasis has been on the anatomical
part, focusing research efforts on the optimization of the CCTA technology. More recently, the focus has been shifting back to the functional part of the CAD equation to compensate for the moderate specificity and positive predictive values of CCTA. The functional evaluation of CAD has its origin in two different paths, one originated from the cardiology and interventional radiology side and the other from the nuclear imaging side (8,9).

Fractional flow reserve (FFR) has been used to measure the functional consequences of specific lesions by measuring a pressure gradient over this lesion, assuming that a drop in pressure will result in a corresponding drop in coronary blood flow and thereby impair the blood flow to the myocardium (10). This technique has been hindered by the high cost and invasiveness of the procedure. More recently, a new approach to calculate FFR non-invasively has been developed, CT derived FFR (CT-FFR). With the use of computational fluid dynamics and optionally the use of artificial intelligence, it is now possible to calculate FFR from regular CCTA images to anatomically and functionally evaluate the significance of a lesion (11). Several studies have proved the excellent diagnostic accuracy of CT derived CT-FFR with the use of AI, either compared to invasive FFR or computation fluid dynamics derived CT-FFR (12–15). The major difference between CT-FFR and invasive FFR is the measurement location. Invasive FFR is measured over a specific pre-determined stenosis, whereas CT-FFR allows the evaluation of CT-FFR values over the entire coronary tree. Although this comes with certain disadvantages, the lack of a reference standard at all locations of the coronary tree, especially at more distal locations, raises certain questions about how to measure CT-FFR in clinical practice (17,18). Being able to distinguish between stenosis specific and location dependent decreases in CT-FFR could increase the accuracy of CT-FFR. Multiple studies have focused on the diagnostic accuracy of CT-FFR, however, besides aiding in the diagnostic process, CT-FFR could also aid in the prognostication of CAD patients. Currently, data on the use of CT-FFR for prognostication purposes is lacking.

The second pathway to combined anatomical and functional analysis is through myocardial perfusion imaging (MPI). MPI started as a technique limited to the molecular imaging techniques such as SPECT and PET, but has become available for CT as a result of technological developments. CT-MPI is a technique which allows for the absolute quantification of myocardial blood flow, directly calculated from the myocardium. Absolute quantification of myocardial perfusion is able to not only quantify lesion specific ischemia but it is also able to identify global ischemia and microvascular abnormalities, in contrast to MPI using other modalities (19,20). Traditionally, CT-MPI was limited by the low temporal resolution and high radiation dose of CT systems, however, on current high-end systems CT-MPI is now possible at equal or even lower radiation doses than the nuclear equivalent.
Inherent to the limited number of acquisitions possible due to radiation dose and the influence of cardiac motion on image quality, CT-MPI acquisitions are made at a specific predetermined time of the cardiac cycle. This is in contrast with the coronary flow, leading to perfusion of the myocardial muscle, which fluctuates in unison with this cardiac cycle. In contrast to most other tissues, blood flow through the coronary arteries reaches its peak during ventricular diastole. This seemingly paradoxical pattern is caused by the contraction of the ventricular myocardium during systole which compresses the subendocardial coronary vessels. The intricate relationship between the cardiac cycle and the corresponding coronary blood flow pattern makes it very difficult for MPI techniques, using only a limited number of acquisitions to capture the perfusion phase. It should be kept in mind that, although it is called myocardial perfusion imaging, it is likely that not only the perfusion phase is imaged but also the arterial and venous filling phase.

One of the issues with CT-MPI being used in a clinical setting is the wide variety of protocols, systems, and models used resulting in a wide range of absolute myocardial blood flow (MBF) values with corresponding ranges of threshold values (21–23). Another issue encountered when comparing CT-MPI to perfusion imaging with other modalities is the significantly lower MBF values measured with CT-MPI (24). One of the major limitations of CT-MPI is the radiation dose given at each time-point acquisition. Because of the additional radiation dose given with each time-point, CT-MPI is currently limited to only several time-points and thus the timing of the dynamic acquisitions becomes crucial, causing the critical points of the inflow and outflow process to be easily missed. Currently, the mathematical models used to calculate MBF are directly extracted from MRI perfusion studies and an optimal model for CT-MPI has yet to be determined. One of the main differences in contrast kinetics between CT and MRI is the fact that the contrast medium used for MRI fractionally diffuses into the interstitial space after the first pass, in contrast to iodine, which shows higher percentages of recirculation. Temporal sampling rate, which is less of an issue in MRI due to the lack of radiation, and the choice of mathematical model, could influence the accuracy of absolute perfusion quantification (24,25).

Although both CT-FFR and CT-MPI focus on the functional analysis of CAD, they visualize different processes. While CT-FFR looks at stenosis specific coronary flow changes, CT-MPI focuses on overall changes to the myocardial perfusion. CT-FRR could play a role in indicating which coronary artery and which stenosis should be targeted by therapy while CT-MPI could additionally detect perfusion defects as a result of non-stenosis specific causes such as microvascular diseases. Several studies have compared the diagnostic accuracy of these two emerging technologies, indicating that both technologies should be used in a complementary fashion (26,27). The direct
relationship between the two, thus far, remains unclear. CT-FFR and CT-MPI can not only be used for diagnostic purposes but could also play a role in the prognostication of CAD patients. However, a combined approach with prognostication as a main goal has yet to be investigated.

With the technological developments making CT-MPI possible came the development of dual energy CT (DECT) systems. DECT uses two different independent energy levels, making optimal use of different spectra at different energy levels. Whereas single-energy only provides morphological information based on the HU values, DECT provides additional functional and material specific information. Technological advances to the current high-end CT systems allow DECT acquisition at radiation doses similar to those of single energy CT and significantly improves the temporal resolution. One of the major clinical applications of cardiac DECT resides in the quantification of iodine content in the myocardium, indirectly visualizing myocardial perfusion (28,29). This brings us to the next and final step in the ischemic cascade, myocardial infarction. With the use of DECT, it is possible to perform tissue characterization by analyzing the iodine content at different acquisitions such as rest, stress, and delayed enhancement acquisitions. This not only allows for the identification of ischemia and infarction but also offers possibilities for the evaluation of extracellular volume, both are processes which were traditionally assessed using cardiac MRI.

Besides technological advancement in the field of medical imaging, another major innovator rapidly changing the field of (cardiac) imaging is artificial intelligence (AI). Medicine is one of the more recent scientific fields to experience the massive influx of machine learning applications. Not entirely beyond expectation, radiology, in which pattern recognition plays a major role, is at the heart of AI developments in medicine (30–32). AI in cardiac CT imaging has the potential to assist with the evaluation of the increasing amounts of data while decreasing the variability, time to diagnosis and treatment, and hospital costs.

Although giant strides have been made in recent years in the field of quantitative cardiac CT imaging, many questions still remain: how to optimize CACS, CT-FFR, and CT-MPI techniques in clinical practice, how do CT-FFR and CT-MPI relate to each other, and how can DECT be used to optimize tissue characterization using CT? An important question covering all of these new technologies is how can AI play a role in any of these processes?
OUTLINE OF THIS THESIS

In light of the aforementioned developments, this thesis will focus on evaluation of these new CT technologies for the quantitative analysis of CAD at different phases of the ischemic cascade for the risk assessment, diagnosis, and prognostication of patients with CAD. It is divided into several parts, each committed to a specific part of the evaluation of CAD, from anatomical to functional evaluation describing different technologies used for these purposes.

Part I of the thesis will focus on coronary plaque and vessel wall analysis. In Chapter 2, an overview of artificial intelligence techniques and their applications is given. Chapter 3 will continue on one of those applications, namely AI based calcium scoring on dedicated ECG-triggered cardiac non-contrast CT acquisitions. Besides using dedicated scans, non-ECG –triggered scans could be used for calcium scoring, which is of specific interest with the growing amount of chest CT scans performed for lung cancer screening. The last chapter of Part I, Chapter 4, will focus on a model based algorithm for plaque characterization used for MACE prognostication.

Subsequently, Part II of this thesis will focus on the next step in the ischemic cascade, coronary flow analysis. In Chapter 5, AI computed CT-FFR in negative patients is explored, with the emphasis of the course of CT-FFR values throughout the coronary tree in relationship to lumen area and HU values. This chapter will give insights into the use of CT-FFR in clinical practice, especially when CT-FFR is given for the entire coronary tree instead of a single location corresponding to invasive FFR. It is assumed that an impaired coronary flow will lead to impairment in myocardial perfusion, however, although there is an indirect correlation, the relationship between these two parameters remains unclear. Chapter 6 and 7 will evaluate the relationship between coronary flow and myocardial perfusion, either to each other or for the prognostication of MACE.

This will take us to Part III of this thesis, which will address some of the fundamental basics of myocardial perfusion analysis. Chapter 8 serves as an overview of current evidence of dynamic CT perfusion studies and CT perfusion protocols and technology. In Chapters 9 and 10, two fundamental technological components of dynamic CT perfusion will be addressed; the temporal sampling rate and the computational model used to calculate myocardial blood flow. The use of Regadenoson as a stressor agent instead of Adenosine with SPECT perfusion as a reference standard will be investigated in Chapter 11.
Impairments of myocardial perfusion will inevitably, without intervention, lead to myocardial damage. Part IV will focus on different techniques to measure and analyze myocardial fibrosis, either in infarcted tissue or in cardiomyopathies. Chapter 12 will focus on rest/stress DECT perfusion imaging and the use of iodine quantification to identify ischemia or infarcted myocardium, while Chapter 13 is a feasibility study on the use of DECT to calculate ECV, which in turn can be used to assess myocardial fibrosis in e.g. patients with cardiomyopathies.

Finally, in Chapter 14, the main results from all chapters will be put into perspective in a general discussion. Recommendations and proposals for further studies will be given in this last chapter.
REFERENCES


CHAPTER 1: GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS
PART I

Coronary plaque and vessel wall analysis