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Automated analysis approaches for coronary CT angiography : labeling, quality assessment and plaque thickness comparison

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CHAPTER 1

General Introduction

CORONARY ARTERY DISEASE

Coronary artery disease (CAD) is still one of the leading causes of death worldwide [1] which is usually caused by the build-up of plaque in the walls of the coronary arteries resulting in limited blood flow to the heart muscle.

Coronary Arteries

Coronary arteries are the blood vessels around the heart which supply blood to different parts of the heart muscle (Figure 1.1). There are two major coronary arteries, the right coronary artery (RCA) and the left coronary artery (LCA). The LCA is further separated into left anterior descending (LAD) and the left circumflex (LCX). Their common part is called the left main (LM) artery. Some side branches, such as septal perforator, obtuse marginal (OM), and diagonals (D) are derived from RCA and LCA.

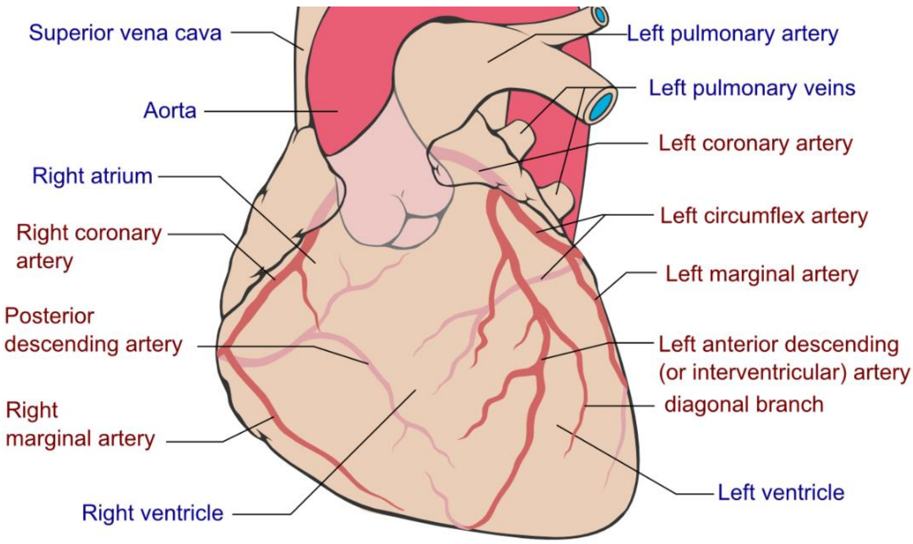


Figure 1.1 Heart and coronary arteries from a right dominance type coronary circulation. Coronary segments are marked with corresponding anatomical names. When posterior descending artery is supplied by left circumflex artery, it is called left dominance type. From: (https://commons.wikimedia.org/wiki/File:Coronary_arteries.svg)

Coronary Circulation

Coronary circulation has major importance in the system circulation since it supports not only the heart but also the entire body. The main artery, RCA or LCX, that supplies the posterior descending artery (PDA) determines the dominance type of the coronary circulation [2]. In the general population, there are three categories of coronary circulations: the right dominant (RD, 86.6% of the population) in which the PDA is supplied by the RCA and is called right posterior descending artery (RPDA); the left dominant (LD, 9.2%) in which the PDA is supplied by the LCX and is called left posterior descending artery (LPDA); and the balanced type (4.2%) in which both RCA and LCX supplies PDA [3]. Figure 1.1 shows a right dominant coronary artery circulations. The anatomical names of corresponding coronary arteries are marked.

Coronary Artery Plaque

Due to several processes, and also depending on life style and age, plaques build up in the coronary arteries, which eventually may result in lumen stenosis. If the plaque grows large enough, a semi-blockage or full blockage of the artery will cause a chest pain or a heart attack (Figure 1.2). Coronary plaques can develop at different locations in the coronary arteries with a different size. Furthermore, a build-up of plaque in the arteries not only puts people at risk for heart and vascular disease but also makes them vulnerable to cancer, kidney, and lung diseases [4].

CAD often develops over decades. An early diagnosis of the plaque location, size and type will help the risk stratification, early treatment, and prognosis. Due to the rapid development of imaging techniques, a more advanced and detailed diagnosis of CAD is available nowadays.

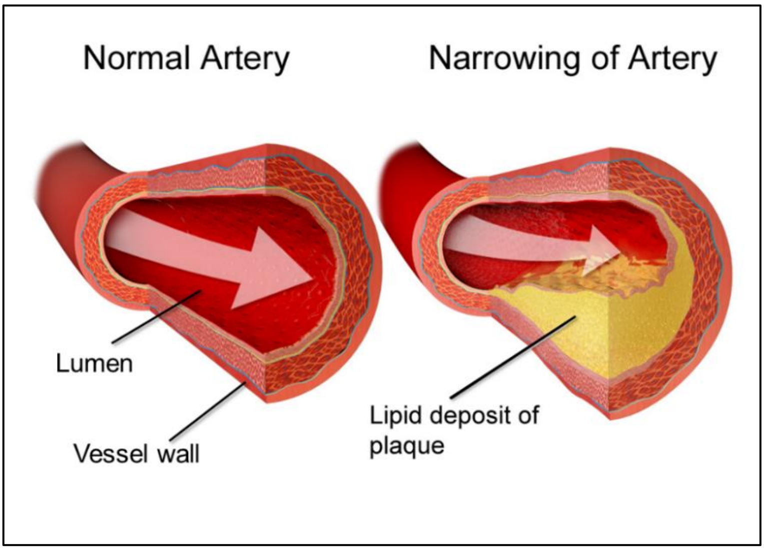


Figure 1.2 Coronary lumen and Vessel wall [5].

IMAGING TECHNIQUES

Different imaging modalities are available for CAD diagnosis and plaque characterization [6, 7]. The choice of the imaging modality depends on the goal and varies among different countries, regions and even hospitals. In the following sections, we categorize the imaging techniques as invasive and non-invasive imaging modality to give a brief introduction.

Invasive Coronary Angiography (ICA)

X-Ray Angiography uses x-ray as imaging source and makes use of that different tissues absorb different amounts of x-rays. To ensure adequate opacification of the coronary lumen, a contrast agent is administered into the arteries by an intracoronary catheter to enhance the lumen. X-ray angiography is still the most commonly used technique in the catheterization laboratories for the visualization of the coronary arteries and to guide the treatment when necessary [8]. However, the vessel wall (plaque) cannot be visualized by X-ray images, which limits its application for CAD early diagnosis. Furthermore, X-ray angiography is limited by its 2D projection of the lumen in a moving coronary arterial tree. The C-arm based x-ray angiography provides views from different viewing angles. Therefore, the angiography images from different viewing angles allows for the possibility of a 3D/4D reconstruction for the coronary arteries [9].

During the last decades, other invasive imaging technologies have been developed, intravascular ultrasonography (IVUS) [10], optical computed tomography (OCT) [11], and near-infrared spectroscopy (NIRS) [12]. They are all catheter-based techniques. A detector is placed inside of the coronary artery with the guidance of the x-ray angiography which enables its ability to evaluate the vessel wall.

Intravascular ultrasonography (IVUS) uses ultrasound as imaging source to provide real-time cross-sectional images with a resolution of about 0.1 to 0.2 mm, which is able to view the vessel wall and enables an early detection of plaques. IVUS is highly accurate for detecting and quantifying CAD and has become an integral tool in the catheter laboratory for the characterization of intermediate angiographic stenosis [10]. IVUS remains the gold standard for plaque quantification [13].

Intravascular optical coherence tomography uses near-infrared (NIR) light, typically with wavelengths of approximately 1.3 μm, as the imaging source in in which a catheter is inserted in to coronary artery [11]. The acquired OCT images provides higher resolution (10-20μm) cross-sectional images compared to IVUS which enables the capability of plaque composition and thin fibrous cap analysis. However, the penetration of OCT is limited due to high light attenuation, which makes OCT only assess the superficial layers of the vessel wall. It also requires blood-free field of view which may add significant complexity to the procedure.

Near-infrared spectroscopy system (NIRS) is based on the principle that different substances absorb NIR light to different degrees at different wavelengths (from 800 ~2500 *nm*) when the light interacts with certain molecular bonds [12]. NIRS is used for the identification of lipid-rich and potentially vulnerable atherosclerotic plaques. The main limitation of NIRS is the lack of information regarding the lumen, plaque anatomy, and the status of the fibrous cap or its attenuation. NIRS is combined with IVUS to enable a complete assessment of patient’s arteries, including vessel size and structure, plaque volume, area, and composition [14].

All of these are invasive imaging techniques which rely on arterial catheterization under the guidance of X-ray to gain direct access of the coronary vasculature. Since these technologies are invasive, they are often used for patients with intermediate or advanced CAD which are candidates to undergo an intervention. For routine check, or stable chest pain doing an invasive check is costly and not patient-friendly.

Noninvasive Coronary Angiography

Although invasive coronary angiography has been the gold standard in establishing the diagnosis of CAD, there is a growing shift towards using noninvasive imaging modalities for more efficient use of the cardiac catheterization laboratory to perform interventional procedures once a diagnosis of CAD has been established.

***Coronary computed tomography angiography* (*CCTA*)** is a noninvasive technique and uses x-ray as imaging source to do a slice scanning which later can be reformatted into a 3D image. To provide a contrast in the coronary artery, a contrast agent is injected into the coronary intravenously. CCTA is widely used for the assessment of patients with suspected CAD because of its high specificity and sensitivity [15, 16]. It provides detailed information about the anatomy of the coronary arteries and the characteristics of coronary atherosclerosis such as the extent of calcifications, the volumetric plaque burden, plaque composition, degree of stenosis and occlusions.

Magnetic resonance angiography (MRA) uses strong magnetic fields to generate images of the organs and therefore does not involve radiation. However, the relatively long image acquisition time and operator dependency have limited the widespread use of coronary MRA. It is not frequently used in coronary arteries since coronary arteries are tortuous and smaller in size, and both the heart motion and respiratory motion affect the image quality [17]. The use of coronary MRA is more on the blood flow of the coronary artery for a functional check [6]. Moreover, most experts and clinical guidelines support the use of coronary MRA only for the assessment of anomalous coronary arteries and coronary artery aneurysms in patients with Kawasaki disease.

Nuclear Medical Imaging Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are nuclear medicine techniques which provide measurements of myocardial disease through functional imaging. SPECT uses gamma emitting radionuclides which can reconstruct 3D images from different 2D images of distribution of radionuclides in the targeted organ taken by a gamma camera from different angles. SPECT allows for a qualitative or semi-quantitative assessment of regional perfusion defects. PET uses positron emitting radionuclides, which are labelled to biological compounds of interest, to generate images of physiological processes [18]. Different from SPECT, PET is able to provide absolute quantitative of myocardial flow and coronary flow reserve. SPECT and PET are often accomplished with the aid of CT scans or MRI scans which are obtained in the same session and provide both anatomic and metabolic information.

It is difficult to make a general conclusion on the optimal imaging technique. The optimal choice for the right modality for diagnosing CAD is a combination of the purpose of the test, patient situation, health care budget and the experience of the doctor.

In this thesis, we are discussing the use of CCTA images in terms of its non-invasively early diagnosis that is fast and has a high resolution together with its feasibility for precise plaque quantification.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY (CCTA)

CCTA is widely used for the assessment of patients with suspected CAD [15, 16]. From 2009, CCTA was introduced as a new, alternative option for emergency department evaluation of non-acute coronary syndrome cardiac chest pain [19]. It provides detailed information about the anatomy of the coronary arteries and the characteristics of coronary atherosclerosis such as the extent of calcifications, the volumetric plaque burden, degree of stenosis and occlusions.

Patient management Despite the non-invasive and high-speed imaging, CCTA has advantages in health care resource utilization which reduced unnecessary hospital admissions and emergency department length of stay [19]. From a point of patient management view, CCTA also enables the long-term prognostic assessment for patients with suspected CAD.

Apart from identifying coronary artery narrowing as the cause of chest discomfort, it can also detect other possible causes of symptoms, such as a collapsed lung, blood clot in the vessels leading to the lungs, or acute aortic abnormalities.

Dose Reduction Strategies The main drawbacks of using CCTA includes radiation and contrast exposure. Various strategies have been proposed to reduce the radiation dose, such as lowering tube voltage, or prospective electrocardiogram-gated tube current modulation, while preserving diagnostic accuracy [20, 21]. Recent developments in low-dose CT reduces the radiation without deteriorate the imaging quality.

Reporting System For standardizing the interpretation and reporting of coronary CT angiography, the first guideline was made in 2009 and then updated in 2014 by the Society of Cardiovascular Computed Tomography Guidelines Committee (SCCT) [22, 23]. In clinical practice, radiologists and cardiologists usually report pathological findings from CCTA images according to the SCCT guidelines in which a coronary artery segment model based on the American Heart Association (AHA) is widely used (Figure 1.1). Recently, a reporting system, named CAD-RADS^{TM} was proposed to standardize the CCTA reporting and facilitate patient management after CCTA [24].

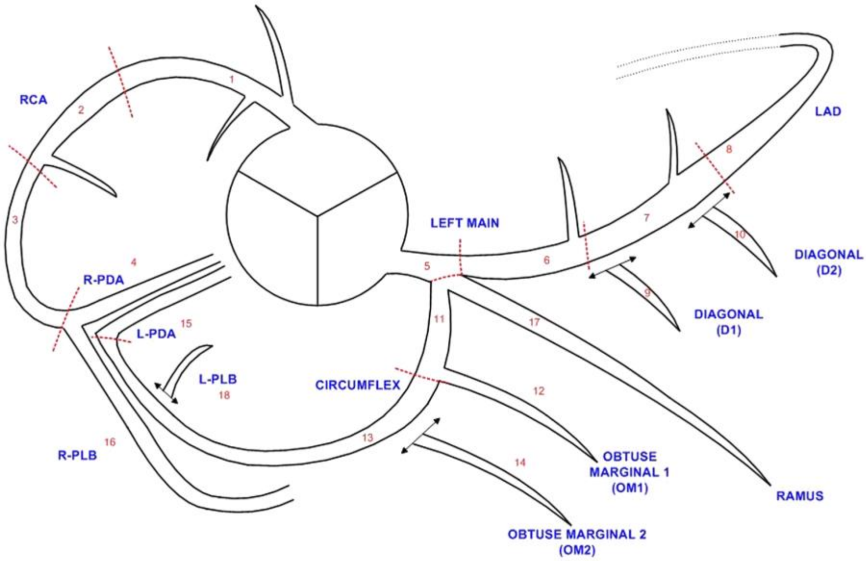


Figure 1.3 Society of Cardiovascular Computed Tomography (SCCT) coronary segmentation diagram. Dashed lines represent division between RCA, LAD, and LCX and the end of the LM. PLB= posterior-lateral branch; PLV= posterior left ventricular branch. Definitions derived and adjusted from the American Heart Association Model. SCCT Guidelines 2014

QUANTITATIVE ANALYSIS ON CCTA IMAGES

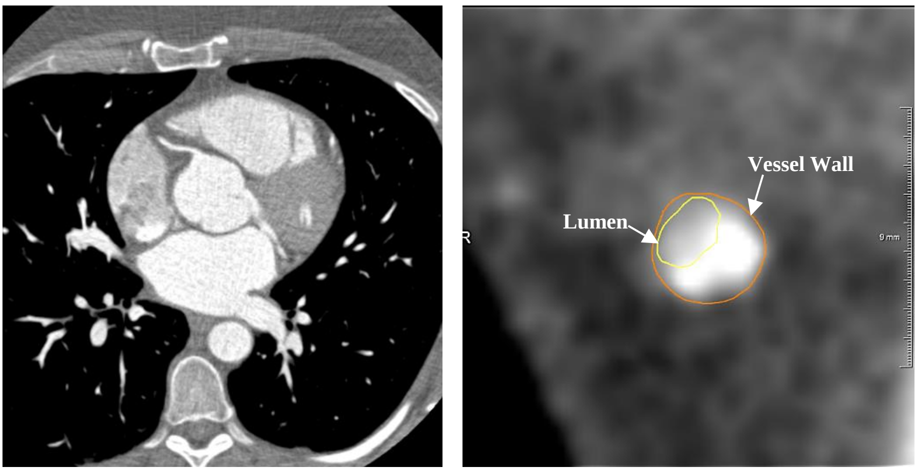
For the purpose of increasing the reproducibility of the analysis on CCTA images, reducing user interaction and manual bias, approaches for quantitative analysis of coronary arteries on CCTA images have been studied during the past decades. In the following section, some approaches to aid quantitative analysis on CCTA images are described.

Coronary Artery Tree Extraction

Coronary artery trees (CATs) are often extracted before doing automatic analysis of coronary arteries on CCTA images. A number of automatic CAT extraction methods have been published in the literature [25-33]. Lesage et al. [34] presented an overview of the previous studies in CAT extractions. Regardless of the specific applied segmentation method, vesselness measurements are often designed to describe the features of the targeted coronary arteries on CCTA images. One of the most widely used vesselness measurements is Frangi's vesselness filter which enhances the long shape tubular structures in the image and is often modified to improve the extraction results [35-37]. Besides feature measurements based on prior knowledge of the appearance of coronary arteries, vesselness features can also be obtained based on machine learning without any prior assumption [28]. More and more CCTA images with experts' annotations enable the possibility of using deep learning related algorithms. Recently, Wolterink et al. [32] presented a work using a convolutional neural network (CNN) based orientation classifier for CAT centerline extraction which shows the feasibility of applying deep learning for vessel feature from image data directly without hand-crafted vesselness representations.

Coronary Artery Lumen and Vessel Wall Contours Detection

One benefit from CCTA is that it enables the visualization of the lumen and vessel wall (Figure 1.4). Marquering et al. [38] presented a method to automatically detect longitudinal and transversal contours for coronary arteries based on the image gradient, and then connect the candidates using a minimal cost approach. Automatic detection of lumen and vessel wall contours for coronary arteries could help the automatic quantification of coronary plaques. After a comparison with the gold standard IVUS, Boogers et al. [39] showed the feasibility of doing automated quantification of coronary plaques on CCTA images using a dedicated registration algorithm.



(a) (b)

Figure 1.4 The coronary CTA image. (a) a slice of a coronary CTA image; (b) a close-up image of the coronary artery on 2D axial view with lumen and vessel wall contour highlighted.

Coronary Artery Plaques Analysis

The location of a coronary artery plaque has different clinical significance. Compared to more distally located lesions, a proximal located lesion has a worse prognosis for patients with acute myocardial infarction [40, 41]. For example, on each coronary segment, a different weight factor is applied in the SYNTAX score which was designed to determine the extent and complexity of CAD [42]. Therefore, it is necessary to do a localization of the stenosis on a coronary artery.

Automated quantification of coronary plaques on CCTA images has become feasible due to the development of automatic extraction, labeling, quality assessment for CATs and lumen and vessel wall segmentation methods [39, 43-46]. Changes of plaques between a coronary artery tree at baseline (*CAT-BL*) and coronary artery tree at follow-up (*CAT-FU*) are assessed on CCTA images to investigate the plaque development after a treatment, or to study the association with long-term mortality [47, 48]. Currently, plaque changes are measured manually [45].

IMAGE PROCESSING CHALLENGES

There are several challenges in extracting, identifying, quality assessment for coronary artery trees and automatic plaque comparison of the coronary arteries on CCTA images.

Coronary Artery Tree Extraction Since vesselness filters for coronary artery extraction are designed based on assumptions about the appearance of the coronary arteries, they may not fully grasp the information available in the data, especially in low-contrast regions of the image due to stenosis. Even with an improved vesselness filter, there are gaps in the filtered vesselness image when there is a low contrast due to a severe occlusion in the coronary artery. Furthermore, surrounding veins could be wrongly extracted as arteries because of their similar appearance to the arteries. These typical situations can create unwanted shorter or longer extractions.

The extracted CATs containing wrong extractions often require corrections from experts. The method in [37] presented a branch searching method to overcome gaps and include disconnected branches. In some studies, statistical models or 3D CAT models were used as prior information to deal with the gaps or early termination of the search. A method called active searching was proposed by Han et al. [49] to solve the discontinuity in the automatically extracted CAT. A statistical branch occurrence location model was used in the study to predict the position of the branch. However, the detection of the discontinuity and different types of vessels in the extracted CAT were not described. Furthermore, the statistical branch occurrence model is used only for the LM artery. Zheng et al. [50] used a 3D coronary tree model to predict the initial position of the major centerlines, but information for side branches was not included.

Identification of Coronary Artery Tree Anatomy Identification of the coronary tree anatomy, i.e. automatically assigning labels to the segments of coronary trees was limited to the RD coronary trees in most previous studies [51-54]. Although ~86% of patients have a RD [3] coronary system, a widely applicable system should also be able to deal with LD coronary trees [55-57].

Another issue is that in most applications, the dominance type of the studied cases is manually determined [53, 58-60]. With the aim for processing large cohorts for multi-center studies, the manual dominance type determination limits the fully automatic processing of the whole pipeline, such as the automatic identification of the extracted coronary artery trees.

Quality Assessment Standardization Even though methods were proposed for coronary artery tree centerline or lumen segmentation, the evaluation measurements for the extracted coronary artery tree are quite limited. The coronary artery centerline extraction challenge at the MICCAI 2008 provided a platform to evaluate coronary artery centerline extraction methods [25]. The evaluation is in terms of the distance from the given ground truth extractions which were limited to the three main arteries and some selected smaller arteries. The standardized evaluation framework sets a benchmark of state-of-the-art techniques while the evaluation for the extracted coronary tree itself is limited, such as the completeness of the tree.

Automatic Analysis of Coronary Plaque Changes Coronary plaque changes between *CAT-BL* and *CAT-FU* are currently manually compared on CCTA images. The corresponding arteries from the *CAT-BL* and *CAT-FU* are first visually assessed from a similar longitudinal viewing angle, and then aligned using anatomical landmarks, for instance, bifurcation points. Afterwards, coronary plaque differences are calculated based on the 2D transversal view and experts visually assess and grade the changes. However, manually selecting a viewing angle and landmarks for the alignment is time consuming and potentially introduces bias. Moreover, calculating plaque changes in 2D does not utilize the 3D topology information.

AIM AND SCOPE OF THIS THESIS

The main focus of this thesis is to develop approaches to help achieving fully automatic analysis of coronary arteries on coronary CT angiography images.

Previous studies have demonstrated the clinical significance of stenosis localization. Therefore, automated lesion reporting and risk stratification requires an automatic coronary identification algorithm. In **Chapter 2**, an automatic coronary artery tree labeling algorithm is presented to identify the anatomical segments for extracted coronary arteries from both RD and LD cases.

CATs are often extracted before the detection and quantifications of coronary arteries. The quality of the extracted CATs is very important since it will affect the successive steps. However, automatically extracted CATs often miss some arteries or include wrong extractions which require manual corrections before further steps. For analyzing a large number of datasets, a manual quality check of the extraction results is time-consuming and labor-intensive. Therefore in **Chapter 3,** a scoring system is developed to assess the CAT extraction quality using the clinical importance of the artery segments described in the AHA model and the completeness of the extracted CAT.

Based on the designed scoring system, it is able to assess the quality of the extracted CAT. Still, experts need to do manual corrections for the extracted CAT before using the CAT for the analysis which are very tedious. **Chapter 4** describes a model-guided method to detect potential incorrect extractions and automatically improve the extracted CAT, and the designed scoring system is used to monitor the improved extraction quality.

Coronary plaque changes between baseline and follow-up coronary artery trees are important for investigating the association of plaque changes after treatment, and studying the association with long-term mortality. Therefore, **Chapter 5** describes a method to automatically measure the plaque thickness changes between *CAT-BL* and *CAT-FU* which allows the automatic comparison of plaque progression or regression.

This thesis ends with a summary of results, a general discussion and a future outlook in **Chapter 6** in English, Dutch and Chinese.