Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

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Chapter 1

General Introduction and Outline of the Thesis

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General Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality and morbidity. Worldwide 3.8 million men and 3.4 million women die of CAD each year.[1] In 2007 11,876 people died of CAD in the Netherlands.[2] Currently approximately 1 in 25 patients in the Netherlands have CAD, and the prevalence is expected to increase by 40% until 2025, due to demographic changes in the Dutch population.

CAD is caused by the development of atherosclerotic lesions in the coronary arteries. The process of atherosclerosis is induced by endothelial dysfunction, inflammation and the influx of cholesterol in the artery wall.[3] This process is mediated by multiple risk factors including age, gender, smoking, hypertension, hypercholesterolemia, diabetes mellitus, obesity, and family history. Formation and early progression of atherosclerosis occurs asymptomatically. Acute symptoms may develop when an atherosclerotic plaque ruptures causing coronary thrombosis and acute coronary occlusion. Stable or chronic symptoms develop due to atherosclerosis progression not resulting in coronary occlusions. As the lesion progresses it may start to block the coronary artery, thereby affecting myocardial blood flow. At first this stenosis is counterbalanced by vasodilatation of the coronary artery. However, as the stenosis progresses further, myocardial perfusion and function decrease and patients start to experience chest pain. Complaints generally become apparent at first during exercise or stress. During rest, adequate myocardial blood flow can usually be maintained, however during exercise or stress the myocardial blood flow can no longer be increased to cope with increased oxygen demand.

Currently many diagnostic tools are used to detect the presence of CAD, varying from clinical assessment, blood markers, and the electrocardiogram (ECG), to invasive and non-invasive cardiac imaging. The latter plays an important role in both diagnosis and risk stratification of patients with suspected or known CAD.

Imaging of CAD

The presence of CAD can be identified by direct anatomic assessment of coronary atherosclerosis and stenosis. In contrast, CAD may also be diagnosed indirectly by assessment of myocardial perfusion and function in rest and during exercise or stress. Several anatomic and functional imaging techniques are currently used, of which the invasive modalities are considered the golden standard.

Invasive imaging

Invasive selective coronary angiography is used extensively as a diagnostic tool in both acute and outpatient settings. Using a transfemoral catheter a contrast agent is selectively injected into the ostium of a coronary artery. Simultaneous fluoroscopy allows for high resolution images of the coronary arteries and of luminal narrowing caused by stenotic lesions.[4] In addition to standard fluoroscopic assessment of coronary arteries, coronary angiography has evolved to a platform for intracoronary imaging and measurement using intravascular ultrasound (IVUS), virtual histology (VH), Doppler flow measurement, and the fractional flow reserve (FFR). IVUS and VH provide a set of transversal ultrasound images of the vessel wall, thereby enabling direct assessment of coronary atherosclerosis. In contrast, Doppler flow and FFR measure coronary blood flow and coronary blood flow reserve and are used to evaluate the hemodynamic effect of lesions detected during preceding coronary angiography.

Non-invasive imaging

Although invasive cardiac imaging techniques are considered the golden standard, these techniques are associated with complications. Although severe complications occur in only a very small proportion of patients, invasive imaging is nevertheless generally restricted to individuals with a high pre-test likelihood of CAD. Non-invasive imaging was developed to identify or rule out the presence of CAD in patients with a lower pre-test likelihood of CAD, and has gained widespread popularity in the last decades. The development of stress echocardiography, single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) has enabled non-invasive evaluation of myocardial perfusion and function. Stress echocardiography uses ultrasound to image the myocardium and can identify patients with CAD by detecting impaired wall motion due to decreased blood flow resulting from a coronary stenosis.[5] SPECT and PET asses myocardial perfusion by use of radioisotope tracers which are injected into the bloodstream. The blood-borne SPECT and PET tracers distribute throughout the myocardium and respectively emit gamma radiation and positrons, which can be detected externally by a gamma camera.[6] A perfusion defect caused by coronary stenosis is indicated by decreased emissions from the corresponding myocardial segments. Sets of images obtained during distinct intervals of the cardiac cycle can be looped to assess wall motion. MRI is also used to assess myocardial perfusion and wall motion, however without the use of ionizing radiation. MRI uses a magnetic field to align the nuclear magnetism of hydrogen atoms in the body. The alignment of these hydrogen atoms are subsequently altered by a radio frequency field which results in the hydrogen atoms producing an electromagnetic signal which can be detected by an MRI scanner.[7] Different tissue types can be distinguished from each other by the different electromagnet signals. To assess myocardial perfusion, MRI contrast agents,

which alter the electromagnetic signal emitted from the myocardium, are injected into the bloodstream.[8]

In addition to these non-invasive functional imaging techniques, non-invasive assessment of coronary anatomy has become feasible with the more recent introduction and rapid technical advances of non-invasive imaging using computed tomography (CT). The CT scanner generates a set of cross sectional images of the body, obtained with an X-ray tube and detector row rotating around the longitudinal z-axis of the body.[9] Non-contrast enhanced CT allows for visualization of coronary calcifications as a marker for CAD, and can quantify the extent and severity of coronary calcification by use of the coronary calcium score (CS). Contrast enhanced CT coronary angiography (CTA) provides direct visualization of the coronary arteries and allows for direct detailed assessment of coronary atherosclerosis and stenosis severity.[9]

Objective and outline of the thesis

CTA is a relatively new imaging technique; the objective of the thesis is therefore to explore the value of CTA for diagnosis and risk stratification of CAD in patients presenting with suspected and known CAD, in order to further define its role in clinical practice. In Part 1 of the thesis the value of CTA for diagnosis of CAD, and its relationship to existing diagnostic imaging modalities is described. Chapter 2 reviews the technique and potential implementation of CTA in clinical practice relative to existing non-invasive imaging modalities. In Chapter 3 the diagnostic accuracy of CTA is studied specifically in patients with an intermediate pre-test likelihood, as this is the population of choice for non-invasive diagnostic imaging strategies. In Chapter 4 multiple non-invasive and invasive cardiac imaging techniques are compared to evaluate their ability to detect CAD. Chapter 5 describes the prevalence of atherosclerotic lesion on CTA in patients with normal myocardial perfusion as assessed on SPECT. In Chapter 6 the relationship between CTA, invasive coronary angiography and FFR is described. Chapter 7 assesses the complementary value of CTA and myocardial perfusion imaging using MRI. In Chapter 8 the predictive value of CTA for perfusion defects on SPECT is evaluated in detail. Chapter 9 describes the effects of patient clinical presentation and pre-test likelihood on the relationship between CS and CTA. In Part 2 of the thesis the value of CTA for risk stratification is evaluated; in addition the prognostic value of CTA is compared to other non-invasive imaging techniques used for risk stratification. A review of this topic is provided in Chapter 10. In Chapter 11 the prognostic value of CTA is compared to the prognostic value of myocardial perfusion imaging using SPECT. Chapter 12 describes the incremental prognostic value of CTA over CS testing. The incremental prognostic value of left ventricular function over CTA is discussed in Chapter 13. In Chapter 14 the prognostic

value of CTA is evaluated specifically in patients with an intermediate pre-test likelihood for CAD. Chapter 15 evaluates the prognostic value of CTA in diabetic patients and compares it to a non-diabetic population. The prognostic value of CTA in smokers compared to non-smokers is discussed in Chapter 16. Future perspectives of CTA are discussed in Part 3 of the thesis. The potential value of CTA for perfusion imaging is reviewed in Chapter 17, and the feasibility of diastolic function assessment using CTA is discussed in Chapter 18.

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