Coronary heart disease on coronary computed tomography angiography: in search of the vulnerable patient

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CHAPTER 1

General introduction and outline of the thesis

The most common cause of death globally is cardiovascular disease.[1] Coronary heart disease or coronary artery disease is the most common cardiac pathology and is currently the third leading cause of death in the world associated with 17.8 million deaths per year.[2] Atherosclerosis, the main risk factor for cardiovascular disease, commences with activation of the endothelium before a cascade of events, namely lipid accumulation, fibrous elements and calcification, triggers activation of inflammatory pathways and narrowing of the vessel.[3] These processes result in an atheromatous plaque, which may cause cardiovascular complications. Based on the degree of diameter stenosis, poor supply of oxygen-rich blood to the heart muscle (ischemia), can lead to symptoms such as angina and dyspnea. The diagnostic evaluation of patients with stable chest pain suggestive of coronary artery disease can be assessed with a variety of tests. Non-invasive imaging tests for detection of ischemia like myocardial perfusion imaging, exercise electrocardiography or radionuclide scintigraphy are often used to determine functionally significant stenosis, based on the severity and extent of inducible ischemia of the myocardium. However, most acute coronary syndromes are caused by low grade coronary stenoses.[4] Atherosclerotic assessment with coronary computed tomography angiography (CCTA) is more frequently used as an alternative non-invasive modality to assess stable symptomatic patients. It has high specificity and sensitivity for the detection of anatomically significant coronary artery disease and provides good risk stratification for future cardiovascular events.[5,6]

Plaque quantification

CCTA is an anatomic diagnostic imaging modality using an intravenous contrast agent, that provides information regarding the coronary artery lumen and wall. The totality of plaque, the 'atherosclerotic plaque burden', the plaque location and plaque morphology can be estimated. CCTA is able to detect non-obstructive coronary artery disease (diameter stenosis <50%), which usually does not correlate with cardiac symptoms or positive stress tests, but identifies patients at an early stage. A majority of patients with a major adverse cardiovascular event have no cardiac symptoms or manifestations of coronary artery disease.[7] The development of events in these patients is often caused by the rupture of highly inflamed or unstable atherosclerotic plaques.[8]

Besides information regarding the atherosclerotic extent, CCTA allows quantification of the coronary arteries to derive compositional plaque analysis, high-risk plaque features, and luminal measures, associated with - independent from plaque burden- clinical outcomes.[9-11] High-risk plaque features on CCTA are the napkin ring sign, lesions with a large necrotic core, spotty calcification and positive remodeling.[12] Plaques with at least two of these features are denoted as high-risk and are associated with acute coronary syndrome.[12,13]

Understanding the nature and rate of plaque progression and identification of which patients are at increased risk of major adverse cardiovascular events is a topic of ongoing research. Given the association with adverse events, atherosclerotic progression - independent from baseline plaque volume - has been proposed as a surrogate marker for MACE.[14] An average absolute plaque progression of 1.0% percent atheroma volume was associated with events.[15,16] Lifestyle, pharmacological therapies and revascularization modify atherogenesis and may stabilize or even regress the disease. Statin

therapy is associated with slower total plaque progression, with specifically a larger progression of calcified plaque and a slower progression of noncalcified plaque.[17] The main predictor of events in patients treated with high-dose statins and low on-treatment LDL cholesterol levels was baseline percent atheroma volume.[14] Which factors are associated with the progression of atherosclerosis despite statin therapy, 'statin non-response', is discussed in Chapter 3.

Pericoronary adipose tissue

Prevention of major adverse cardiac events is challenging as many of the plaque ruptures in coronary arteries arise from lesions with less than 50% stenosis.[18] Consequently, the identification of vulnerable lesions at an early stage becomes more relevant. Pericoronary adipose tissue (PCAT), a biomarker associated with vascular inflammation, might improve risk stratification.[19,20] Vascular inflammation is a key factor in coronary atherosclerotic plaque formation, progression and rupture and affects the differentiation, proliferation and lipolysis of the adipocytes in the fatty tissue around the coronary arteries.[19, 21-24] This leads to smaller adipocytes with lower intracellular lipid content which is correlated with higher Hounsfield units, or attenuation values, on CCTA. The feasibility of PCAT attenuation obtained with CCTA and vascular inflammation detection has been shown.[19,25,26] Significant different PCAT attenuation values have been identified between coronaries with and without atherosclerosis, in culprit and non-culprit lesions and between flow-limiting and non-flow-limiting stenosis.[25-28] In Chapter 2 we discuss PCAT attenuation values evaluated in coronaries without atherosclerosis to establish reference values.

Epicardial coronary artery lumen volume to left ventricular mass

Cardiac CT enables the calculation of the ratio of the total epicardial coronary artery lumen volume to left ventricular myocardial mass (the V/M ratio) as well. The V/M ratio is considered a parameter capable of revealing a potential physiological imbalance between myocardial demand and coronary blood supply. Reduced V/M ratios are associated with reduced myocardial blood flow, more extensive coronary artery disease, and lesion-specific fractional flow reserve <0.80.[29-31] An abnormal low V/M ratio might also be expected in patients with high blood pressure as hypertension has been associated with reduced myocardial perfusion reserve.[32-41] Sustained elevated afterload in hypertensive patients causes left ventricular hypertrophy which is associated with an increase in myocardial oxygen demand and a reduction in maximal coronary vasodilator reserve.[42-47] The decrease in maximal vasodilator reserve causes a reduction of peak myocardial flow per unit mass of myocardium and could lead to ischemia during increased myocardial metabolic demands. Factors contributing to the reduction in maximal flow can be primary alterations of coronary vascular tone, an increase in diastolic myocardial wall tension (which could lead to an increase of coronary vascular resistance), or the development of ventricular hypertrophy without concomitant neovascularization.[48] In addition, perivascular and interstitial deposition of fibrillar collagen is found in hypertrophied left ventricles, and the amount of myocardial collagen is increased, leading to impaired ventricular pumping capacity.[49,50] Whether the reduced coronary flow reserve in hypertensive patients is caused by a reduced V/M ratio will be discussed in Chapter 5.

Outline of the thesis

Of all the imaging techniques used in the field of cardiology, this thesis focuses on the role that CCTA may have in the diagnosis, evaluation and risk stratification of coronary artery disease.

Chapter 2 describes values of PCAT, a 'sensor' of vascular inflammation, in patients without coronary artery disease. In Chapter 3 plaque progression on serial CCTA is measured and factors associated with plaque volume progression despite the use of statins are presented. In Chapter 4 we describe the sex- and age-specific differences and interactions in the onset of atherosclerosis and risk for major adverse cardiovascular events using the Leiden CCTA risk score, a comprehensive score that incorporates plaque extent, composition, severity and location into a single value. Chapter 5 investigates the coronary volume to left ventricular mass ratio obtained by CCTA in patients with hypertension. It is a parameter that investigates the relation between coronary vasculature and myocardial mass and capable of revealing physiological imbalance when present.

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