Introduction

Background

Cardiovascular diseases are responsible for 30% of all deaths worldwide and are the number one cause of deaths globally. Cardiovascular diseases caused an estimated 17.3 million deaths in 2008 [1]. Around 40% of these cardiovascular deaths are due to coronary heart disease. It is projected that coronary heart diseases will remain a leading cause of morbidity and mortality for many years to come [2].

Atherosclerosis, the main underlying pathologic process for coronary heart diseases, is a chronic disease state of the coronary arteries that slowly develops over decades before becoming clinically significant. Its pathophysiology is complex, including inflammatory and immunological events which are considered to be of central importance in the initiation and progression of atherosclerotic plaques [3,4].
Gradual chronic progression of coronary atherosclerosis may result in luminal narrowing causing symptoms of angina. However a more acute scenario exists wherein an abrupt change in plaque status causes rapid decrease in luminal patency [5].

Pivotal in these acute scenarios is the formation of thrombus, usually triggered by rupture or erosion of a vulnerable coronary plaque. Following rupture of the fibrous cap covering the atherosclerotic plaque the thrombogenic material in the core of the plaque becomes exposed to the arterial lumen. This causes platelet aggregation and the formation of thrombus. A clinically asymptomatic scenario may follow due to thrombotic sealing of the rupture. In ST-elevation myocardial infarction (STEMI) red thrombus formation often leads to acute vessel occlusion, whereas in non-ST-elevation myocardial infarction (NSTEMI) a non-occluding (mural) platelet rich thrombus is formed [6,7].

Timely diagnosis and initiation of reperfusion therapy, by means of pharmacological therapy and percutaneous reperfusion, are essential in these acute presentations of coronary artery disease in order to minimize myocardial damage [8,9]. Restoring blood flow in the infarct related artery is therefore essential, but unfortunately optimal epicardial patency does not guarantee complete and sustained reperfusion of the infarcted myocardium [10]. With an open epicardial artery, impaired flow in the microvascular compartment is predictive of myocardial infarction (MI) size, left ventricular function and mortality [11].

Monitoring simple and readily available variables such as timelines of reperfusion and epicardial and myocardial perfusion, using angiographic imaging, may aid the interventional cardiologist to identify patients who are at higher risk for future adverse events. It provides the opportunity to select the right combination of treatments for those patients in order to optimize outcomes.

An acute coronary syndrome is the most important clinical advent of atherosclerotic

disease. However, before an acute scenario occurs the slow progressing nature of atherosclerosis gives a unique opportunity in identifying the existence and the extent of atherosclerotic disease. Consequently, it allows the prospect of preventing future myocardial damage. Non-invasive imaging of the coronary arteries with computed tomography (CT) has the ability to detect coronary artery disease. Potentially this method may aid the cardiologist in search of patients with atherosclerotic disease that are most likely to develop acute coronary syndromes in the future and also identify the population in which strict primary prevention may be warranted.

Although atherosclerotic disease is likely to affect the whole coronary system, plaques prone to become unstable are not diffusely present and are only limited in number [12]. Because of its closer approach and higher resolution invasive intravascular imaging of atherosclerotic plaques may better differentiate individual plaque characteristics. Whereas CT may assist in finding a patient at risk, intravascular imaging may help in identifying the individual plaque at risk of developing future events. In this thesis we aimed to assess the value of different imaging modalities, invasive as well as non-invasive, in the evaluation and management of patients with acute coronary syndromes.

Outline of thesis

In **part 1** we focus on value of readily available monitoring variables, such as time to reperfusion, time of onset of symptoms and myocardial perfusion in patients with STEMI. With lengthening of time to reperfusion (ischemic time) the presence of microvascular perfusion decreases, resulting in increased MI size [13,14]. Timely reperfusion of the infarct-related coronary artery early after STEMI is an important factor in the improvement of outcomes. Although ischemia damages the myocardium, it is viable in part early after onset of symptoms and may be salvaged by rapid restoration of perfusion [14,15]. In previous studies, best clinical results of reperfusion by primary percutaneous intervention (PCI) were observed in patients treated within 90 to 120 minutes after symptom onset [13,14,16]. However, advances in treatment, using thrombus aspiration and pharmacological triple antiplatelet therapy during and around the PCI, have resulted in improvement of myocardial reperfusion and clinical outcomes [17-19]. These novel treatment methods may influence the time window for obtaining optimal reperfusion and clinical outcomes in STEMI patients treated by primary PCI. In **chapter 2** we studied the impact of total ischemic time on myocardial perfusion and clinical outcomes in a contemporary cohort of patients with STEMI treated with primary PCI, thrombus aspiration, and triple antiplatelet therapy

The onset of STEMI is not evenly distributed during a twenty-four hour period.

From prior research it has been known that the onset of symptoms of STEMI exhibit a circadian rhythm with peak incidence in the morning hours [20]. However, clinical outcomes seem to differ as well during the twenty-four hour period, depending on the time of onset of symptoms. Recent evidence has emerged that the time of symptom onset of STEMI is significantly associated with MI size, independent of time to reperfusion [21,22]. MI size reflects the amount of myocardial injury as a result of ischemia and is related to clinical outcomes. The time-of-day dependence of MI size also implies a circadian variation in vulnerability of the myocardium to ischemia [21,22]. This may be in turn caused by a circadian variation in myocardial perfusion. In **chapter 3** we explored if the time of symptom onset influences myocardial perfusion and its relation to MI size and subsequent outcomes in a large cohort of STEMI patients.

In **part 2** of this thesis we focus on the use of non-invasive and invasive imaging methods which may be helpful to the cardiologist in guiding cardiac interventions.

Cardiac CT has emerged as a non-invasive imaging modality allowing anatomical imaging of the heart. In particular, the potential of CT visualizing the coronary artery lumen and wall non-invasively has gained tremendous interest. Indeed, CT coronary angiography may be performed to assess coronary artery stenosis in symptomatic patients with suspected coronary artery disease [23,24]. Moreover, CT coronary angiography may potentially be useful for guiding coronary interventions and in the evaluation of the results of treatment. In addition, 3D anatomical information obtained during the examination may be clinically useful in guiding interventions of the cardiac valves or treating rhythm disorders. In **chapter 4** we provide an overview of the current applications of cardiac CT, discussing the areas in which cardiac CT may replace invasive imaging techniques and areas in which cardiac CT may be useful in guiding cardiac interventions.

About 3 to 5% [25] of patients that present as an acute MI have normal coronary arteries on invasive coronary angiography (ICA). This group of patients with acute myocardial infarction and angiographically normal coronary arteries is broadly recognized and described in several series. The pathogenetic mechanisms that cause AMI in these patients are unknown. Outward remodeling of rupture prone atherosclerotic plaques without visible luminal narrowing on ICA have been suggested as underlying cause[26]. Other proposed mechanisms are coronary dissection, endothelial dysfunction, embolism and vasospasm. In **chapter 5** we aimed to assess the presence and characteristics of atherosclerotic plaques on CT coronary angiography in patients with acute MI who have a completely normal coronary angiogram on ICA.

CT coronary angiography enables visualization of the vessel wall offering valuable information about the burden of coronary artery disease. This may provide prognostic

information as well as ability to assess the disease process. Identification of circulating immune-inflammatory markers that are associated with the atherosclerotic disease process in coronary arteries may provide additive information. The relation of neutrophil counts, neutrophil/lymphocyte ratio and other immune-inflammatory markers, with plaque burden assessed by CT coronary angiography was investigated in **chapter 6**.

Rupture or erosion of a coronary plaque containing a large necrotic/lipid core and/or a thin fibrous cap resulting in luminal thrombosis have been linked to the development of coronary events [7]. In preliminary studies with CT coronary angiography it has been observed that the presence of non-calcified plaque component is associated with the development of coronary events [27]. Accordingly, it has been speculated that non-calcified tissue containing plaque on CT coronary angiography might represent rupture prone plaques [28]. However, the ability of CT coronary angiography to discriminate between components of non-calcified plaque is limited and remains challenging [29]. Invasive coronary plaque characterization may be performed by optical coherence tomography (OCT) and intravascular ultrasound (IVUS) with high spatial resolution. Coronary artery lumen and the presence of thrombus can be accurately observed on OCT as compared to histology [30]. Moreover, a good correlation between geometrical and compositional coronary plaque characteristics has been observed between CT coronary angiography and IVUS in patients presenting with stable angina pectoris [31,32]. Nevertheless, to date no data are available on to which extent coronary artery thrombus contributes to the amount of non-calcified tissue of the plaques on CT coronary angiography in patients presenting with NSTEMI. In **chapter 7** we investigated the ability of CT coronary angiography and IVUS to differentiate between characteristics of the culprit lesion in vivo with OCT serving as the standard of reference.

During PCI microembolization of fragmented atherothrombotic material from the culprit lesion may cause additional myocardial damage [33]. Manual thrombus aspiration (TA) is effective in retrieving atherothrombotic debris [19,34]. The systematic use of TA in STEMI patients is associated with less distal embolization, an improved post-procedural myocardial perfusion and improved prognosis at 1-year follow-up [19,35]. Thus far, TA studies have been focusing mainly on patients with STEMI. One small study performed in patients presenting with NSTEMI who underwent PCI within twenty-four hours after clinical presentation demonstrated that TA is associated with high rates of retrieval of thrombotic material [34]. Whereas TA is frequently performed in patients with visible thrombus on ICA, thrombus is often not detectable on ICA [19,34]. We investigated the efficacy of TA, evaluated with OCT in patients presenting with NSTEMI after initial conservative therapy, which is described in **chapter 8**.

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