Dynamics of intracoronary thrombosis in STEMI and sudden death patients

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General introduction and thesis outline
General Introduction

Cardiovascular disease is a significant public health problem in Western countries and is becoming an increasingly significant problem in developing countries. Atherosclerosis is responsible for many of the severe manifestations, including acute myocardial infarction (AMI), heart failure and stroke. The clinical events caused by progressive atherosclerosis currently remain the primary cause of death in Western society. An estimated 36,000 cases of new AMI occur in the Netherlands each year.

Natural history of atherosclerosis

Human atherothrombotic disease is a dynamic process and it is a continuum of complex biological processes. Atherosclerotic plaques take many decades to develop and the process of plaque formation begins early in life in relation to recruitment and retention of circulating lipids and inflammatory cells in the intimal layer of the vascular wall. The natural history of atherosclerosis involves the progression of early lesions to more complex plaques that are responsible for the majority of acute ischemic coronary events.

It is widely accepted that the initiation of disease-related plaques begins as what is referred to as pathological intimal thickening (PIT). These lesions arise from smooth muscle cells enriched in an environment of proteoglycans and collagen with discreet pools of lipid. Although there are many detailed autopsy studies describing the various transitional lesion morphologies, little is known about how human atherosclerosis progresses from early to more advanced plaques, marked by the formation of a necrotic core. Extracellular matrix degradation together with macrophage cell death and early necrosis is believed to mark the conversion of PIT into an early fibroatheroma, which are considered the first of the advanced lesions. Further, during the evolution towards an early fibroatheromatous lesion, an overlying layer of fibrous tissue (fibrous cap) becomes identifiably that separates the central necrotic core from the arterial bloodstream. The combination of greater macrophage infiltration and apoptotic death together with hypoxia-induced necrosis promotes development into a late fibroatheromatous lesion. An atherosclerotic plaque with a large necrotic core and an overlying thin fibrous cap (<65 mm) infiltrated by macrophages and T-lymphocytes characterizes thin-cap fibroatheroma (TCFA). The large necrotic core may be calcified with areas of hemorrhage (Table 1). Inflammation and the production of cytokines, tissue proteolysis by matrix metalloproteinases (MMP), and apoptosis of smooth muscle cells are suggested as critical factors in plaque progression and fibrous cap thinning. However despite many theories, the precise mechanism(s) responsible for fibrous cap thinning are still not known. Lesions with a thin, fibrous cap are those that are most likely to rupture and therefore, often referred to in the literature as “vulnerable plaques”. Vulnerable plaques have a high propensity to develop plaque rupture followed by thrombosis (atherothrombosis), leading to clinical events.
Table 1. Morphological characteristics of culprit and rupture-prone plaques in cases of sudden coronary death.

<table>
<thead>
<tr>
<th>Plaque type</th>
<th>Necrotic core, (%)</th>
<th>Cholesterol clefts, (%)</th>
<th>Macrophages, (%)</th>
<th>Mean no. of sections with intraplaque hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrocalcified</td>
<td>15 ± 20</td>
<td>4 ± 6</td>
<td>6 ± 8</td>
<td>&lt;0.05 ± 0.6</td>
</tr>
<tr>
<td>Erosion</td>
<td>14 ± 14</td>
<td>2 ± 5</td>
<td>10 ± 12</td>
<td>0</td>
</tr>
<tr>
<td>TCFA</td>
<td>23 ± 17</td>
<td>8 ± 9</td>
<td>14 ± 10</td>
<td>---</td>
</tr>
<tr>
<td>Rupture</td>
<td>34 ± 17*</td>
<td>12 ± 12†</td>
<td>26 ± 20‡</td>
<td>2.5 ± 1.3§</td>
</tr>
</tbody>
</table>

p value  * 0.003 vs. erosion, † 0.002 vs. erosion, ‡ <0.001 vs. erosion, § <0.01 vs. fibrocalcified, erosion and fibrocalcified

TCFA = thin cap fibro-atheroma. With permission of Dr. Virmani and Dr. Kolodgie.

The study of the vulnerable plaque phenotype and its detection has attracted considerable interest in recent decades with the idea that, because if we could identify these sites before a rupture event take place, we could then treat them by interventional means or even medically to prevent cardiovascular events. This could drastically reduce both morbidity and mortality. Therefore, many invasive and non-invasive imaging modalities are being developed to accurately characterize structural and morphologic characteristics of the atherosclerotic plaques. Important morphology for the identification of TCFA is the presence of a large necrotic core, thin fibrous cap, and macrophage infiltration of the fibrous cap to signify the degree of inflammation. The value of several invasive imaging techniques, such as intravascular ultrasound and optical coherence tomography, providing morphological information of the plaque that reflect its vulnerability are currently being investigated.

Pathophysiology of acute myocardial infarction

Acute myocardial infarction (AMI) results from myocardial damage following a decrease or complete cessation of coronary blood flow. ST-elevation myocardial infarction (STEMI) usually occurs when a thrombus forms on a ruptured atheromatous plaque and totally occludes an epicardial coronary artery, resulting in myocardial necrosis. The understanding of the pathophysiology of AMI begins in 1844 with the first historical description of the concept of plaque rupture. Although several leading researchers emphasized the role of thrombosis in AMI and coronary thrombi were a frequent finding at autopsy, the causative nature of thrombosis in the pathogenesis of AMI was contested for decades. It was not until 1980 that angiographic evidence was provided that intracoronary thrombi play a causal role in the pathogenesis of acute coronary occlusion in AMI. Autopsy studies by the laboratory of Dr. Virmani have revealed that plaque rupture is the primary underlying cause of luminal thrombosis responsible for provoking AMI and sudden cardiac death. Plaque rupture of a “vulnerable” plaque is responsible for 60% to 70% of acute coronary events. As mentioned above the co-called TCFA is generally considered as the substrate and therefore, ruptured
plaques typically consist of a large necrotic core with an overlying thin ruptured fibrous cap. Rupture of the fibrous cap leads to luminal thrombosis because of contact of platelets and inflammatory cells with the highly thrombogenic necrotic core. Plaque erosion is another significant but less frequent cause of AMI and sudden death, occurring in 25% to 40% in acute coronary events. Plaque erosion shows a luminal thrombus with an underlying base rich in proteoglycans and smooth muscle cells with minimal inflammation. Further, most underlying atheromateous plaques are devoid of a necrotic core, but when present the core does not communicate with the lumen because of a thick fibrous cap. The least common cause of AMI is the calcified nodule.

Importantly, plaque disruption and thrombus formation do not always result in a major symptomatic coronary event. Plaques may rupture, thrombus may develop but blood flow remains unaffected and the vessel heals without clinical sequelae. Although clinically silent, these so-called healed plaque ruptures, contribute to stenosis progression. Davies forwarded the concept that plaque progression beyond 40-50% cross sectional luminal narrowing occurs secondary to clinically silent repeated plaque ruptures. The number of old plaque ruptures parallels an increase in lumen narrowing of plaques. Similarly, Virmani et al reported that 61% of hearts from sudden coronary death victims have healed plaque ruptures and only 11% of acute plaque ruptures are virgin ruptures. Thus, most of the plaque ruptures are initially covered by mural thrombi and did not cause clinical symptoms. The mural thrombi may organize in just 3 to 4 days, a process histologically characterized by ingrowth of smooth muscle cells and overgrowth of endothelial cells, and later on by deposition of collagen and microvascular ingrowths. Further, episodic subclinical ruptures result in significant increase in plaque burden and negative remodeling. Based on these autopsy tissue observations it was presumed that, in many cases of acute ischemic events, the fatal occlusion of an artery was preceded by an ongoing process of arterial thrombosis and arterial wound healing (Figure 1).
Figure 1: In many cases of acute ischemic events, the fatal occlusion of an artery is preceded by an ongoing process of arterial thrombosis and arterial wound healing.

Treatment of STEMI
The goals of acute management of STEMI are to prevent mortality, relieve symptoms, prevent progression of disease, and minimize loss of myocardial muscle and function. Thrombolytic therapy was a major step forward in the treatment of STEMI, and further progress was done when percutaneous coronary intervention (PCI) was introduced.27, 28 Nowadays, early reperfusion therapy by primary PCI (PPCI) in an experienced center is the number one recommendation in the management of STEMI.29 Based on the available evidence, as compared with a strategy of balloon angioplasty, a strategy of routine coronary stenting during PPCI is superior by reducing the need for target vessel revascularization.30-32 Therefore, 85% of PPCIs involve stent implantation and in the current interventional era, both coated (drug-eluting) stents and non-coated (bare-metal) stents are widely used.

The primary goal in reopening an infarct-related artery by PPCI is the restoration of myocardial tissue-level perfusion, which can now be achieved in 95% of patients.33 However, one of the most important remaining therapeutic challenges in STEMI is the establishment of normal myocardial perfusion in all patients. In a sizable proportion of patients (30%), PPCI does not achieve complete myocardial reperfusion at tissue level, in spite of normal epicardial coronary artery blood flow.34 This condition is known as “no-reflow”. Series of consistent data have clearly shown that suboptimal myocardial reperfusion is associated with larger infarct size, increased predisposition to ventricular arrhythmias, heart failure, cardiogenic
shock, recurrent MI, and death.\textsuperscript{35-37} Thus, persistent impairment of myocardial perfusion has a strong negative impact on outcome, negating the potential benefit of PPCI. Suboptimal myocardial perfusion is a complex phenomenon and potential pathogenetic mechanisms in the individual patient are a variable combination of distal embolization of atherothrombotic debris, ischemia injury, reperfusion injury, and susceptibility of coronary microcirculation to injury. Various studies have shown that distal embolization of atherosclerotic debris is responsible for a substantial part of clinically observed no-reflow.\textsuperscript{38, 39} Henriques and Silva-Orrego et al. reported an incidence of distal embolization in patients treated with PPCI of approximately 15 to 19%.\textsuperscript{40-41} The high frequency of suboptimal myocardial reperfusion after PPCI and its association with extension of myocardial injury and poor prognosis has resulted in the development of various mechanic and manual devices to protect the microvasculature from distal embolization. Over the last decade, numerous randomized controlled trials have utilized devices to prevent distal embolization, including distal embolic protection devices, mechanical aspiration devices, and manual aspiration devices.\textsuperscript{42-46} It has been hypothesized that protection of the distal microcirculation during PPCI should result in improved TIMI 3 flow and myocardial perfusion. These improvements should in turn result in reduced infarct size and preserved left ventricular function, which ultimately leads to reduced mortality. Although the value of thrombus aspiration in the setting of PPCI is thoroughly investigated in the recent years, it remains unclear whether it results in a significant improvement of myocardial reperfusion and clinical outcome.

Up to this point, insights in the mechanisms of coronary thrombosis causing AMI mainly come from detailed analyses of underlying plaque morphologies in necropsy specimen from sudden cardiac death victims.\textsuperscript{4, 6, 16, 23, 24, 33} One of the first randomized trials in STEMI patients undergoing PPCI with thrombus aspiration showed that atherothrombotic material could be obtained in approximately three-quarter of these patients.\textsuperscript{45} The present thesis shows that aspirated atherothrombotic material, obtained during PPCI from patients with STEMI, provides an unique opportunity for the histopathological investigation of culprit lesions. This has significantly expanded and integrated the insight in the pathogenesis of acute myocardial infarction obtained by autopsy studies.

Prognosis after STEMI

As a result of advanced revascularization strategies and optimal medical therapy mortality and morbidity has substantially declined in patients with STEMI in developed countries over the past 20 years.\textsuperscript{48} However, there still remain patients at high-risk of complications and adverse clinical events. The ability to differentiate between patients at high- and low-risk may be a valuable tool to optimize the use of different (adjunctive) treatment strategies, which may enhance patient outcomes. Risk assessment may not only be helpful in guiding clinical care as well as for risk adjustment when performing other observational and quality improvement studies. Even in patients with STEMI, for whom initial therapeutic options
are well-defined, accurate risk stratification has an important and integral role for patients on early therapeutic decision making. Physicians have the difficult task of making decisions regarding admission, interhospital transfer, and treatment and identifying patients at high-risk for death and adverse events. Several measures can be implemented in the process of risk assessment, including clinical judgment, electrocardiographic and echocardiographic findings, PCI-related characteristics, and the presence of biomarkers. Many research efforts are being directed towards identification of predictors of poor outcome, and currently, several validated patient-based risk scores are recommended by the American College of Cardiology/American Heart Association and the European Society of Cardiology for early risk stratification in patients presenting with STEMI. Overall, the individual ability of these scores to predict mortality is somewhat variable. In addition, an increasing number of novel serum biomarkers such as N-terminal pro-brain natriuretic peptide (NT-pro-BNP), glucose, C-reactive protein (CRP), creatinine or estimated glomerular filtration rate (eGFR) have been identified to provide powerful prognostic information regarding short- and long-term mortality in patients admitted for AMI. Combining multiple biomarkers seems to provide incremental prognostic information to single-biomarker assessment only and increases the accuracy of the test. However, though a multimarker approach using several biomarkers and clinical risk factors may be advocated for improving risk stratification, the best combinations for predicting prognosis still need to be defined.
Outline of this thesis

This thesis will first focus on the histopathological features of aspirated intracoronary atherothrombotic material and accompanied prognostic implications in STEMI patients undergoing PPCI with thrombus aspiration. Next, this thesis encompasses several morphological studies on atherosclerosis in sudden death victims.

**Part I** focuses on the histopathological characteristics of intracoronary thrombi in patients with STEMI. In Chapter 2, we describe the histopathological characteristics of atherothrombotic material obtained in a large consecutive cohort of STEMI patients treated with PPCI and thrombus aspiration at our institution. In Chapter 3, we used the aspirated atherothrombotic material to study the relation between (micro)calcifications and intraplaque inflammation. Chapter 4 addresses the temporal changes in angiogenesis in aspirated intracoronary thrombi and provides more insight in the dynamics and timing of healing processes of a disrupted plaque.

**Part II** describes several studies in which we aimed to clarify the relationships between thrombus aspiration, thrombus age, serum biomarkers, ST-segment recovery, and clinical outcome. Chapter 5 describes the prognostic value of thrombus age in STEMI patients treated with PPCI and thrombus aspiration presenting within 12 hours after onset of symptoms. The purpose of the study presented in Chapter 6 was to determine the predictive power of thrombus age for 1-year mortality in relation to 5 serum biomarkers and established clinical risk factors. The association between ST-segment recovery and thrombus age is evaluated in Chapter 7. In Chapter 8 thrombus aspiration as definitive treatment is described in a selected small group of STEMI patients. Finally, we focus on ‘failure’ of thrombus aspiration devices. The predictors as well as the prognostic value of not reaching/crossing the ‘culprit’ lesion by the device and the inability to obtain atherothrombotic material are detailed in Chapter 9.

**Part III** concerns 3 morphological studies on atherosclerosis and complications in sudden (cardiac) death patients. The purpose of the study presented in Chapter 10 was to investigate the natural progression of human coronary plaques from PIT to late fibroatheroma in human coronary artery lesions. Chapter 11 explores whether thrombus maturation depends on the underlying ‘culprit’ plaque morphology, plaque rupture or plaque erosion. In the final chapter of this thesis, Chapter 12, we describe a case report presenting a fatal case of stent thrombosis. The report addresses the challenging management of patients with an indication for oral anticoagulation as well as an indication for (drug-eluting) stent implantation.

Finally, we summarize our findings and a general discussion of the finding of this thesis is presented in the context of ongoing research, including conclusions and some future directions for subsequent clinical research in patients with STEMI (**Part IV**). Ultimately, understanding the histopathology of acute plaque rupture, coronary thrombus formation, thrombus healing and subsequent occlusive coronary thrombosis may lead to the identification of patients with coronary disease at risk of STEMI. In addition, adjunct therapies in combination with PPCI for STEMI may be tested for the benefit of patients, resulting in better outcomes.
References

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