Pathomorphological and physiological characteristics of coronary artery disease

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Introduction and outline
INTRODUCTION

Coronary artery disease is the principal cause of mortality in Western Europe and the US. [1] Effort related chest pain, angina at rest, acute myocardial infarction, and sudden cardiac death are the major clinical manifestations of coronary atherosclerosis. These stable or acute coronary syndromes are caused by atherosclerotic plaques developing in the vessel wall, thereby compromising the vessel lumen. The resulting vascular narrowing or "stenosis" leads to impairment of sufficient blood flow and oxygen supply to the contracting cardiac muscle. Atherosclerosis is a multi-causal disease, which progresses with age and is subject to several clinical risk factors, such as smoking, hypertension, hyperlipidemia, diabetes mellitus and a positive family history. [2] Developing atherosclerosis may lead to a variety of coronary plaques and stenosis configurations [Figure 1], which may lie silent or cause clinical symptoms. Clinical research interest in this area centers around the following questions: When is a stenosis associated with complaints of chest pain and causing myocardial ischemia and what type of atherosclerotic lesion is responsible for an acute myocardial infarction and do these lesions differ from those which cause effort related angina? In this thesis, both pathomorphological and functional aspects of coronary atherosclerotic disease have been studied.

Coronary Plaque Morphology and Inflammation

Recognition of the significant role of inflammation in development of atherosclerosis has dramatically changed our understanding of the pathophysiology of coronary artery disease in the last decade. [3-7] Basic research has established an elementary function of inflammation in all stages of atherosclerotic disease, starting from endothelial dysfunction and fatty streak formation to advanced complex and ruptured plaques and subsequently, thrombotic involvement. [5] Coronary atherosclerosis is initiated by endothelial dysfunction including upregulation of adhesion molecules and an increased permeability of the vessel wall to lipids, leucocytes and monocytes. [5] Macrophages and smooth muscle cells transform into foam cells by fagocytosis and accumulation of lipids. In addition, T lymphocytes and smooth muscle cells migrate into the neointima and contribute to the formation of a so-called 'fatty streak'. Expansion of the lipid core of the plaque is stimulated by death of lipid laden foam cells. A large necrotic core with an overlaying fibrous cap is a characteristic feature of an advanced unstable lesion [Figure 2A]. Activated macrophages and T lymphocytes produce numerous growth factors and proteases with proteolytic activity, which are capable of destabilizing the fibrous cap. [3] These inflammatory cells often accumulate in the shoulder region of the cap, the site where plaque rupture frequently occurs [Figure 2B]. [8] Involvement of pro-coagulant factors, which stimulate platelet adherence and aggregation, may lead to a superimposed clot formation and occlusion of the coronary artery. [3, 9, 10] The ensuing acute coronary syndromes or cardiac death are often the first manifestation of this chronic and progressive, and ultimately lethal disease.
Developing atherosclerosis

**INTRODUCTION**

**Figure 1** Schematic illustration of developing atherosclerosis. Initial changes occur in the endothelium, the inner layer of the vessel wall. (A) First, endothelial dysfunction occurs characterized by a reduced dilator response to metabolic or pharmacological stimuli. (B) Increased endothelial permeability and up-regulation of leukocyte and endothelial adhesion molecules cause migration of lipoproteins and inflammatory cells into the vessel wall. (C) Formation of a fatty streak, which predominately consists of foam cells (lipid-laden monocytes and macrophages), T lymphocytes, and migrated smooth-muscle cells. (D) Accumulation of foam cells in the fatty streak underlie to a more complicated type of lesion. An atheroma consisting of a mixture of inflammatory and apoptotic cells, lipid, and debris has been developed. (E) Further progression leads to a so-called "vulnerable plaque", which is characterized by a necrotic core with an overlying thin fibrocellular cap with accumulation of inflammatory cells at the edges. (F) Fibrous cap rupture, which occurs often at the edge of the thin fibrous cap due to proteolytic enzymes released by activated inflammatory cells. Consequently, thrombus formation may cause occlusion of the coronary artery, which may lead to myocardial infarction and sudden cardiac death.

However, not all atherosclerotic lesions develop into unstable plaques. Abundant collagen synthesis and smooth muscle cell proliferation have stabilizing effects, and determine whether a plaque will be stable or vulnerable [Figure 2C]. [6, 11, 12] Figure 3 shows examples of non-ruptured stable (A) and unstable (B) atherosclerotic plaques, the latter demonstrating marked infiltration of macrophages. Our present knowledge of the elementary role of an inflammatory process for the onset of plaque rupture in atherosclerotic coronary lesions primarily stems from autopsy based studies. [8] However, the introduction of directional coronary atherectomy catheters [Figure 4] has provided a unique opportunity to directly investigate the role of inflammation in atherosclerotic plaques of patients. Initial studies have demonstrated significant differences in the extent of plaque inflammation between patients with stable or unstable angina. [13-15] Coronary lesions of patients with unstable angina or myocardial infarction contain more macrophages and T lymphocytes compared to coronary lesions of patients with chronic stable angina. These studies provided additional support of the hypothesis that infiltration of inflammatory cells is crucial for the onset of unstable coronary syndromes.
**Figure 2**

(A) Schematic illustration of a cross-section of a vulnerable plaque. A large lipid core covered by a thin fibrous cap is a typical characteristic of a vulnerable plaque. The lumen of the coronary artery is often well preserved despite a large plaque volume, due to outwards growth of the vessel (positive remodeling).

(B) Schematic illustration of a cross-section of a plaque rupture. The fibrous cap is disrupted at the shoulder site, where many inflammatory cells have infiltrated. The thrombus with large atheroma extends into the vessel lumen and may occlude the coronary artery completely. This is the typical lesion of unstable angina and myocardial infarction.

(C) Schematic illustration of a cross-section of a stable plaque. A thick fibrous cap covers the lipid core, if present.

**Figure 3**

A) Cross-section of a vulnerable atherosclerotic plaque, showing abundant infiltration of macrophages (asterisk), predominantly the lipid core and at the shoulder site of the cap.

B) Cross-section of a stable atherosclerotic plaque, showing few macrophages (asterisk).
Nevertheless, there is still limited information regarding the in vivo evaluation of this atherosclerotic process. Therefore, the goal of the first part of the thesis was to investigate the role of plaque inflammation on the presentation of coronary syndromes and on the clinical outcome following percutaneous interventions.

Coronary Revascularization

Percutaneous transluminal coronary angioplasty (PTCA) is increasingly performed for symptomatic treatment of coronary artery disease. [16] However, the performance of PTCA is not without risk. Periprocedural complications occur infrequently, but include death (0.3%), myocardial infarction (1.5%), emergency coronary artery bypass grafting (0.4%), and puncture site hematoma (1%). Moreover, the 'Achilles heel' of PTCA is the occurrence of restenosis in up to 50% of cases within the first six months after balloon angioplasty. [17-21] The process of restenosis starts directly after angioplasty by subacute elastic recoil. The 'healing process' of the arterial wall following angioplasty continues with platelet aggregation, mural thrombus formation, and development of a neointima by invasion and amplification of smooth muscle cells. Finally, remodeling of the vessel wall occurs. The introduction of coronary stents in the beginning of the nineties has led to a reduction of the restenosis rate. [22, 23] However, despite limited remodeling and recoil, smooth muscle cell proliferation still occurs within the stent. A large effort has been exerted to find a solution to manage in-stent restenosis, which is a serious problem. [22] Therefore, it is of utmost importance to identify the culprit coronary lesion, which causes myocardial ischemia and needs to be treated.
Non-Invasive Assessment of Coronary Stenosis Severity

The functional significance of coronary narrowings in terms of causing myocardial ischemia is generally assessed by a non-invasive diagnostic stress test. Exercise electrocardiography, myocardial perfusion scintigraphy (MPS) and dobutamine stress echocardiography (DSE) are frequently used. [24] However, exercise electrocardiography has its limitations in elderly and women, frequently yielding non-conclusive results. [24] MPS is hence used to overcome the limitations of exercise electrocardiography. MPS has a high diagnostic and prognostic value for coronary artery disease. However, MPS is limited in assigning reversible perfusion deficit to vascular territories of different narrowed coronary arteries. [25] DSE has a similar diagnostic accuracy as MPS. However, DSE is in particular dependent on experienced laboratory technicians and the physician's analysis. [26] Moreover, there is still variability when qualitative assessment is standardized and DSE has a low sensitivity in multivessel coronary artery disease. [26, 27] In clinical practice, the noninvasive stress tests are frequently inconclusive, while other objective evidence of myocardial ischemia is lacking in the majority of patients prior to revascularization procedures.

Figure 5 Illustration of the discrepancy between the angiographic and the physiological severity of coronary lesions. A wide range of measurements of a hemodynamic parameter (coronary flow velocity reserve) are observed for intermediate coronary lesions, i.e. 40 to 70 percent diameter stenosis.
Figure 6 Schematic illustration of the coronary morphology on angiography, showing two cross-sections of coronary arteries with plaque and their corresponding angiographic images in one view. A similar preserved lumen is present in both arteries despite a different angiographic severity from the 'bottom view'; 50% diameter stenosis (DS) in Fig. 6A and 10% DS in Fig. 6B. The angiographic view from the left side shows no stenosis at all, despite a severely diseased vessel.
Figure 7 The angiographic and intravascular ultrasound (IVUS) images of a severely diseased left circumflex coronary artery (LCx). The main stem seems to be normal on angiography (A), however, IVUS shows a large plaque from 12 to 5 o'clock (B). An ulcerated plaque has been located at angiography at the proximal part of the LCx, which corresponds to a soft plaque covered by a thin fibrous cap (C), with the rupture site further downstream (D). The mid portion of the LCx shows no disease on angiography, however a concentric fibrous lesion is present (E). At the distal part of the LCx, both coronary angiography and IVUS show no disease (F).
Evaluation of Coronary Stenosis Severity by Angiography

While coronary angiography is the gold standard for documentation of the presence and extent of coronary artery disease, its limitations in assessing the functional significance of coronary stenoses have been well recognized. [28, 29] The discrepancy between angiographic and physiological severity exists especially for coronary lesions of intermediate severity, i.e. stenoses with 40-70% diameter reduction [Figure 5]. [30] Therefore, management of intermediate lesions during cardiac catheterization is equivocal. The limitations of coronary angiography are in part explained by a phenomenon called 'illusion of luminology' [Figure 6A and 6B]. This denotes that evaluation of coronary morphology by angiography is imprecise and dependent on the angle of view, since coronary angiography shows only a two-dimensional projection of a three-dimensional vessel. [28] Intravascular ultrasound imaging overcomes these limitations in part by providing accurate information on the extent of coronary atherosclerosis within the vascular wall, thus facilitating documentation of the dynamic process of atherosclerotic disease [Figure 7]. [31] However, this technique is expensive and requires accurate operational skills for appropriate interpretation. As a result, this technique is not frequently applied for dia-

Figure 8 Schematic illustration of the relation between proximal coronary arterial perfusion pressure and coronary blood flow with (solid lines) and without (dashed lines) a stenosis. The solid arrows indicate the coronary flow reserve with (CFRs) and without (CFRn) a stenosis.
gnostic purposes and, in general, is used for guidance of coronary interventions. In the evaluation of stenosis severity, both imaging techniques share the drawback that the association between morphologic descriptors of a stenosis and its functional consequences is weak and more direct approaches are necessary to assess the physiologic significance of a coronary lesion. [16-23]

**Functional Coronary Lesion Severity**

Coronary revascularization is required when stenosis severity has reached that level when coronary flow becomes so impaired that myocardial oxygen supply cannot meet demand. Under normal conditions, coronary blood flow may increase above a baseline level due to exercise, which causes an increase in myocardial oxygen demand, or various pharmacological stimuli. The coronary arterioles, the major resistance vessels, can dilate to increase myocardial blood flow (velocity) up to six fold. [30, 32] The reserve capacity, calculated as the ratio of maximum to resting coronary blood flow is named coronary flow reserve. [33] Figure 8 illustrates the effect of the presence of a stenosis on coronary flow reserve.

The development of guide wires with a tip diameter of only 0.014 inch equipped with miniaturized pressure- or flow velocity-sensors has led to the introduction of hemodynamic measurements in the diseased coronary vessel. [34, 35] The derived physiological parameters as a measure of functional coronary stenosis severity are useful for patient management, facilitating ad hoc PTCA and evaluating the results after angioplasty and/or coronary stent placement. [36] Pressure-based myocardial fractional flow reserve (FFR), coronary blood flow velocity reserve (CFVR) and relative coronary blood flow velocity reserve (RCFVR) are parameters that are used in clinical practice. [37] FFR represents the maximal flow through a stenosed vessel divided by the maximally possible flow in the absence of the stenosis. CFVR is defined as the ratio of hyperemic to baseline flow velocity and RCFVR is defined as the ratio of CFVR measured in the coronary artery with a stenosis divided by the CFVR in a normal reference artery. Figure 9 illustrates the assessment of these intracoronary derived parameters. FFR, CFVR and RCFVR have been compared in various studies with non-invasive stress tests and the results demonstrated a good agreement between these hemodynamic parameters and the presence or absence of reversible ischemia. [36] Commonly used threshold values indicative of functionally significant coronary lesion are 2.0 for CFVR and 0.75 for FFR. [36] Despite the diagnostic value of these hemodynamic parameters, several limitations have been recognized. First, CFVR is dependent on changes in heart rate, blood pressure and myocardial contractility. [38, 39] The RCFVR was introduced to overcome this limitation of CFVR through normalization within a patient. [40, 41] However, this requires additional instrumentation in a normal coronary artery, if present. It should also be recognized that most of the studies were performed in patients with stable angina, single vessel disease and normal left ventricular function. Information is
Figure 9: Illustration of an intermediate coronary lesion (arrow) in the proximal part of the left anterior descending coronary artery (LAD, A). The intracoronary pressure derived fractional flow reserve (FFR) value of 0.83 indicates a hemodynamically non-significant (>0.75) lesion (B). Coronary blood flow velocity reserve (CFVR), defined as the ratio of maximal hyperemic flow velocity (h-APV) to baseline flow velocity (b-APV), distal to this stenosis has a value of 3.7, which is also above the threshold (>2.0) of functional significance (C). Reference CFVR is 4.2 and the calculated relative CFVR (defined as CFVR_{artery with stenosis}/CFVR_{reference artery}) is 0.88 (=3.7/4.2) (D).
limited for patients with the probability of microvascular disease due to acute myocardial infarction, unstable angina, hypertension, ventricular hypertrophy, diabetes mellitus and diffuse disease. The aim of the second part of the thesis was to evaluate the diagnostic and prognostic value of combined intracoronary pressure and flow velocity measurements in an unselected large patient population scheduled for elective PTCA.

Outline of the thesis
The first part of the thesis concerns the evaluation of coronary plaque inflammation, as determined by immunohistochemical analysis of culprit coronary lesions, in patients with stable and unstable coronary syndromes. Macrophages, T lymphocytes and C-reactive protein are the major inflammatory mediators that have been used to determine the presence of inflammation. Chapter 2 deals with the evaluation of the relation between coronary plaque inflammation and clinical and angiographic characteristics of coronary artery disease. In Chapters 3 and 4, the extent of plaque inflammation and smooth muscle cell proliferation was evaluated in atherectomy specimens of patients with restenosis and in-stent restenosis lesions. The role of tissue C-reactive protein in relation to presentation of stable and acute coronary syndromes is evaluated in Chapter 5 and Chapter 6 deals with the significance of plaque inflammation for the occurrence of recurrent coronary events after coronary angioplasty.

The second part of the thesis concerns the evaluation of functional stenosis severity using intracoronary pressure and flow velocity measurements in patients with stable coronary artery disease. Coronary lesions with a wide range of angiographic severities were hemodynamically evaluated using sensor-tipped guide wires. Chapter 7 deals with a comparison between outcomes of established functional parameters (FFR, CFVR and RCFVR) and myocardial perfusion scintigraphy in a large patient population with multivessel coronary artery disease. The role of microvascular resistance in the relationship between FFR and CFVR and its association with stenosis severity are evaluated in Chapters 8 and 9. In Chapter 10, the diagnostic accuracy of FFR and CFVR to detect reversible ischemia is compared to a new parameter based on a combination of both intracoronary pressure and flow velocity, the hyperemic stenosis resistance index. A comparison of the prognostic value of FFR, CFVR and the hyperemic stenosis resistance index with respect to major adverse cardiac events after deferral of PTCA in intermediate coronary lesions is provided in Chapter 11. Chapter 12 concerns the additional prognostic value of biochemical markers of inflammation (C-reactive protein) for clinical decision-making and management of patients with hemodynamically non-significant coronary lesions.
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CHAPTER 1


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