Improved assessment of functional severity of coronary artery stenosis by analysis of combined intracoronary pressure and flow velocity signals
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Chapter 1

General introduction
Abstract

The heart requires a continuous supply of blood, for which it has developed a network of coronary arteries that run over the surface of the heart and branch into smaller vessels penetrating the heart muscle. Blood flow to the heart muscle may be impeded by local narrowing of an epicardial artery. This blood flow impediment can result in a mismatch between oxygen supply and demand, and, if left untreated, in myocardial ischemia. Invasive treatment can be performed by either bypass surgery or percutaneous coronary intervention. In the latter case, the stenosis is expanded by intracoronary balloon dilatation, followed by stent placement to prevent recoil.

In order to adequately select patients for such a procedure, hemodynamic measurements can be performed to determine the functional severity of a stenosis. Despite the large progress made in the past decennia on functional assessment of a stenosis, there is still room for diagnostic and therapeutic improvement. This chapter describes some fundamental principles of coronary physiology that form the basis for functional evaluation of a stenosis in the catheterization laboratory. Present shortcomings in the assessment of the physiological significance of a coronary artery stenosis and adequate patient selection are introduced.
Coronary anatomy

In order to maintain blood flow throughout the body, the heart itself needs to be supplied by blood as well. This blood supply of the heart is facilitated by its own vascular system, the coronary circulation (Figure 1). Oxygen-rich blood is transported via the ascending aorta and the sinuses of Valsalva into the left and right coronary ostium. The left main stem arises from the left coronary ostium and bifurcates into the left circumflex and the left anterior descending artery, while the right coronary ostium gives rise to the right coronary artery. The left coronary arteries perfuse the left atrium and ventricle and the interventricular septum, while the right coronary artery perfuses the right atrium and ventricle and the posterior part of the left ventricle. These vessels lie on the epicardial surface of the heart and give rise to the transmural vessels, which penetrate the myocardium and branch into a wide network of small vessels forming the coronary microcirculation. The small arteries (diameter <400 µm) and arterioles (diameter <200 µm) together are called coronary resistance vessels, since they form the primary site of coronary resistance and play an important role in the regulation of coronary blood flow.

Figure 1: Anterior view of the heart and epicardial arteries.

Coronary blood flow in a healthy heart

In a healthy heart, coronary blood flow is well controlled and matched to meet its oxygen requirement by adapting the smooth muscle tone in the vessel wall of the coronary resistance arteries, thereby altering the lumen diameter of these vessels. The regulation of coronary blood flow under different circumstances can best be described by the coronary pressure-flow relationship as depicted in Figure 2. The two major determinants of coronary blood flow are coronary arterial pressure and myocardial oxygen consumption. For a given coronary arterial pressure, coronary blood flow increases with myocardial oxygen consumption, a phenomenon called metabolic adaptation. However, at a constant level of oxygen consumption, coronary blood flow is relatively independent of arterial pressure, referred to as coronary
autoregulation (1). These two mechanisms are interrelated and may even be due to the same control mechanism. The relatively horizontal line denoted as ‘Autoregulation I’ represents the relationship between coronary pressure and blood flow for a certain oxygen consumption level, the condition under which flow is kept constant despite alterations in coronary pressure, and is referred to as the autoregulation plateau. The line denoted as ‘Autoregulation II’ is the autoregulation plateau for an increased level of oxygen consumption. The steepest line represents the relationship between coronary pressure and blood flow when the resistance vessels are maximally dilated, meaning there is no tonus in the vessel wall, a condition known as maximal hyperemia. Under this circumstance, the blood flow becomes linearly dependent on coronary pressure. The ratio between the maximal and basal coronary blood flow is called the coronary flow reserve (CFR) and represents the capacity of the heart to increase flow to an increase in oxygen demand.

**Coronary artery disease**

Cardiovascular disease is the world’s leading cause of death (World Health Organization, 2008). Within the EU, coronary artery disease (CAD) accounts for almost 2 million deaths on an annual basis. Atherosclerosis, which is the underlying disease process of CAD, is a systemic disease of the arterial vessel wall. Starting from young adulthood, it develops asymptotically over several decades (2) due to the fact that the vessel wall has the capacity to remodel. Influx and accumulation of lipids form a plaque within the vessel wall. This plaque formation will initially lead to compensatory enlargement of the vessel, thereby preserving the inner lumen of the vessel, while in a later stage of the disease progressive plaque formation results in inward remodeling (3). In that latter stage, the vessel becomes obstructed. The different stages of atherosclerotic plaque formation are depicted in Figure 3.

**Effect of a stenosis on coronary blood flow and myocardial perfusion**

In an undiseased coronary artery, i.e. when there is no stenosis, pressure along the epicardial vessel is assumed to remain relatively constant. A small but insignificant reduction in perfusion pressure can be present due to viscous losses according to the Poiseuille law (Figure 4). The presence of an epicardial narrowing however results in an additional resistance to coronary blood flow, which can result in a significant reduction of coronary perfusion pressure distal to the stenosis. This reduction in coronary perfusion pressure is the result of a pressure gradient (ΔP) over the stenosis, which is caused by an increase in viscous losses along the stenosis according to the law of Poiseuille and exit losses at the throat of the lesion according to the law of Bernoulli, and is dependent on blood flow.

Blood is a viscous medium, implying that there are shear stresses between the different layers of the medium as it moves forward, resulting in a frictional resistance. This resistance is proportionally related to the length of a vessel and the viscosity of blood and inversely related to the fourth power of the diameter (Figure 4). The reduction in lumen diameter along the narrowing therefore results in a pressure loss
**Figure 2:** Coronary pressure-flow relationship. CFR, coronary flow reserve.

**Figure 3:** Different phases of atherosclerotic plaque development. On the left a normal coronary artery is shown, followed by the outward remodelling demonstrated in the middle figure and finally the inward remodelling phase of atherosclerosis resulting in obstruction of blood flow as shown on the right.

**Figure 4:** Viscous pressure loss ($\Delta P$) within a vessel is dependent on the viscosity ($\mu$) of the fluid and the length ($L$) and lumen diameter ($D$) of the vessel. $Q$, blood flow.
over the stenosis due to a higher frictional resistance. A reduction in cross-sectional area of the vessel also implies a higher blood flow velocity at the narrowing since the same volume of blood has to pass through a smaller lumen area at the same unit of time (Figure 5).

This acceleration of blood results in a higher kinetic energy density in the stenosis which is realized at the expense of potential energy density (which is equal to pressure) according to the law of energy preservation (Figure 6). Hence, the increase in kinetic energy density implies a reduction in pressure in the stenosis which is proportional related to the density of blood and inversely related to the fourth power of the diameter reduction. Theoretically, the pressure should recover beyond the stenosis as the diameter becomes normal again. However, the higher velocity jet leaving the stenosis causes flow separation and eddies in the reattachment zone (Figure 6). The additional friction within this disturbed flow pattern prevents a complete pressure recovery at the exit of the lesion.

Viscous losses are linearly related to blood flow, while exit losses increase with the square of blood flow and in combination this results in a curvilinear relationship between the pressure gradient and coronary blood flow described as $\Delta P = a \cdot Q + b \cdot Q^2$ (Figure 7). This relationship represents a unique characterization of the hemodynamic effect of a stenosis.

The reduction in perfusion pressure due to the pressure gradient over the stenosis results in a diminished coronary flow reserve, as is illustrated in Figure 8. Under baseline conditions and for a certain level of myocardial oxygen consumption, autoregulation will keep coronary blood flow at a relatively constant level. Reduced perfusion pressure in the presence of a stenosis is compensated by decreasing microvascular resistance. The effect of the stenosis pressure gradient becomes evident under hyperemic conditions. In the absence of a stenosis, the pressure gradient at resting and hyperemic blood flow is insignificant. However, in the presence of a stenosis, the pressure gradient will increase with increasing flow, as depicted by the red line, resulting in a lower maximum flow at hyperemia, thereby reducing CFR.

Hence, the obstructed coronary artery limits blood flow to the myocardium, which can result in a shortage of adequate myocardial oxygen supply. Left untreated, this condition can result in clinical complications such as myocardial ischemia.

**Patient selection for percutaneous coronary intervention**

Revascularization of stenotic coronary arteries can be performed by either coronary artery bypass grafting during cardiac surgery or by percutaneous coronary intervention (PCI). The choice of a particular revascularization method depends, among other reasons, on the balance between the short-term convenience of a less-invasive PCI and the long-term advantages of a more invasive surgical approach (4). However, regardless of the selected method, revascularization of an obstructed epicardial coronary artery aims to relief myocardial ischemia (4). In contrast to patients with unstable CAD, where myocardial ischemia is obvious and life-threatening, for
Figure 5: Decreased lumen diameter within a stenosis ($D_s$) does not only increase the viscous pressure loss but also increases the blood flow velocity within the stenosis ($v_s$), since the blood flow through the vessel remains constant. $A_{prox}$, lumen area proximal of the stenosis; $A_s$, lumen area within the stenosis; $D_{prox}$, lumen diameter proximal of the stenosis; $v_{prox}$, blood flow velocity proximal of the stenosis; $Q$, blood flow.

$$Q = A_{prox} \cdot v_{prox} = A_s \cdot v_s = \text{constant}$$

Figure 6: The sudden expansion of the vessel at the throat of the stenosis causes flow separation and eddies, which result in a pressure loss. $\rho$, density of the medium; $D_{prox}$, lumen diameter proximal of the stenosis; $D_s$, lumen diameter within the stenosis; $\Delta P$, pressure gradient over the stenosis; $P_{prox}$, pressure proximal of the stenosis; $P_s$, pressure within the stenosis; $Q$, blood flow; $v_{prox}$, blood flow velocity proximal of the stenosis; $v_s$, blood flow velocity within the stenosis.

$$P_{prox} + \frac{1}{2} \cdot \rho \cdot v_{prox}^2 = P_s + \frac{1}{2} \cdot \rho \cdot v_s^2 = \text{constant}$$

$$\Delta P = \frac{1}{2} \cdot \rho \cdot \left(1/D_s^4 - 1/D_{prox}^4 \right) \cdot Q^2 = b \cdot Q^2$$

Figure 7: The pressure gradient ($\Delta P$) over a stenosis is the sum of the viscous losses along a stenosis, which are linearly related to coronary blood flow ($Q$), and the losses at the exit of the stenosis, which are quadratically related to coronary blood flow. Together, they result in a curvilinear relationship between pressure gradient and coronary blood flow, thereby uniquely characterizing the hemodynamic effect of a stenosis.

$$\Delta P = a \cdot Q + b \cdot Q^2$$

Figure 8: Effect of a stenosis on coronary flow reserve. Without a stenosis, coronary flow can increase at an almost constant coronary perfusion pressure to almost four-fold (CFR$_{N}$). In the presence of a stenosis, the increasing pressure gradient ($\Delta P$) over the stenosis lowers the maximal flow that can be achieved at hyperemia, thereby causing a decrease in coronary flow reserve (CFR$_{S}$).
patients with stable angina and in particular those with multivessel disease, it is not so obvious which stenosis indeed causes myocardial ischemia (4). For these patients, current guidelines recommend functional assessment of a stenosis to select patients for revascularization. It has been demonstrated that angiographic images cannot fully characterize the hemodynamic effects of a stenosis (5, 6). The presence of reversible myocardial ischemia can be detected prior to cardiac catheterization by non-invasive perfusion imaging techniques. Alternatively, invasive measurements of intracoronary hemodynamics can be performed to obtain clinical indices during the catheterization procedure to identify functionally significant stenoses (4). Clinical indices of functional stenosis severity currently accepted are based on the assessment of either flow velocity or pressure signals, of which the pressure-derived fractional flow reserve (FFR) is the most frequently used index. Despite its diagnostic improvement compared to angiography, FFR is obtained prior to PCI in only 6% of patients in the USA (7).

Current limitations in patient selection for PCI based on intracoronary hemodynamics

Axial measurement location of sensor-equipped guide wires
Current practice guidelines specify that sensor-equipped guide wires used to obtain hemodynamic signals for the derivation of functional indices of stenosis severity should be positioned at least 2 cm beyond the lesion (6). However, it is not known whether choosing a more distal measurement location affects these hemodynamic signals. In clinical practice, the distance between the actual measurement location and the throat of the stenosis can vary quite well, since it is important to find a good and stable flow velocity signal. A second issue is the use of flow velocity as surrogate for coronary flow, based on the assumption that a decrease in cross-sectional area of branching vessels is matched by a reduction in perfusion territory, thereby making flow velocity rather constant throughout the epicardial coronary bed. For a good interpretation of pressure and flow velocity based clinical indices of stenosis severity and microvascular resistance, it is important to know whether these signals or clinical indices are affected by the axial measurement location at which they are obtained.

Requirement of maximal hyperemia
The clinical indices presently in use critically depend on the achievement of maximal vasodilation (8, 9). Most frequently, injection of adenosine is used for this purpose (10). However, there is a current debate on the dose of adenosine required to achieve this maximal vasodilation (8, 11). Furthermore, adenosine is not readily available in every catheterization laboratory. The introduction of clinical indices that do not require maximal vasodilation may therefore improve the adoption of functional stenosis assessment in daily practice.

Increased microvascular resistance in the presence of coronary artery disease
Atherosclerosis is a systemic disease which also extends to the coronary microcirculation affecting coronary microvascular resistance (12). The clinical application of coronary microvascular resistance as a measure of the extent of
Introduction

Microvascular disease is hampered by the controversy regarding its definition. This controversy is related to the role of collateral flow contribution to total myocardial flow (13, 14). This discussion is rather relevant since the concept of FFR is based on a simplified model that assumes microvascular resistance to be minimal and constant and not be affected by the presence of a stenosis (15). However, FFR depends on microvascular resistance. For a given stenosis, a lower value of minimal microvascular resistance causes a decrease in FFR and may result in a false positive quantification of the functional stenosis severity, while a higher value of microvascular resistance causes an increase in FFR which may result in a false negative diagnosis. Additionally, the presence of an elevated minimal microvascular resistance in patients with CAD has also important consequences for the interpretation of clinical indices and functional tests used to identify the presence of myocardial ischemia. In the end, the goal of revascularization therapy is relief of myocardial ischemia which is the result of both epicardial and microvascular contributions to disturbed myocardial perfusion.

Combined assessment of intracoronary pressure and flow velocity

Recent advancements in the technology of sensor-equipped guide wires have enabled the simultaneous assessment of coronary pressure and flow velocity (Figure 9), which can give a more complete view of the coronary circulation and can provide clinical indices that do not require maximal hyperemia.

The combined assessment of intracoronary pressure and flow velocity enables the determination of vascular resistances and the separation between epicardial and microvascular contributions to total myocardial resistance. The use of dual-sensor equipped guide wires in daily clinical practice to assess both functional lesion severity as well as microvascular resistance may therefore enhance adequate patient selection for PCI.

![Figure 9: Dual-sensor guide wire, enabling the simultaneous assessment of pressure and flow velocity.](Figure9.png)

Aim of this thesis

The aim of the present thesis was to improve patient selection for PCI by 1) proposing new clinical indices for the assessment of functional stenosis severity using combined measurements of intracoronary pressure and flow velocity, that do not require
maximal vasodilation of the coronary vascular bed, and 2) by determining the association between hyperemic microvascular resistance (HMR) distal to epicardial narrowing and the presence of reversible myocardial ischemia.

**Thesis outline**

**Chapter 2** In addition to invasive measurements, diagnostics and treatment decision can be improved by non-invasive assessment of regional perfusion measurements. However, all these different modalities in isolation often result in conflicting treatment recommendations. This chapter reviews the role of the development of perfusion models of the heart used for the interpretation of underlying physiological mechanisms of CAD on clinical decision making. Model development enables the integration of information from these different modalities and can generate simulation frameworks, thereby providing better insights into the coronary physiology that may result in improved patient care.

**Chapter 3** As hemodynamic measurements obtained during cardiac catheterization form the basis of clinical indices of functional stenosis severity and the identification of coronary microcirculatory dysfunction, understanding these basic principles of coronary physiology is required for a proper interpretation of these physiological measurements. In this chapter, a review is given on the basic characteristics of coronary hemodynamics as described by pressure-flow relations, coronary microvascular resistance and myocardial perfusion distribution in the normal and diseased heart.

**Chapter 4** In this study, we assessed whether intracoronary pressure, flow velocity and derived indices of functional stenosis severity and microvascular resistance are affected by differences in axial measurement location distal to the lesion. Secondly, this study assessed whether flow velocity throughout the epicardial vascular bed is independent of segmental lumen diameter, implying a constant flow velocity in all branch segments available for hemodynamic measurements as proposed by the Square law, or whether it is linearly dependent on segmental lumen diameter as proposed by Murray’s law.

**Chapter 5** In this chapter, a new, vasodilator-free functional index of stenosis severity, the baseline stenosis resistance (BSR), obtained during resting conditions, was introduced to circumvent the need of adenosine to assess functional stenosis severity. This study compared the diagnostic accuracy of BSR to that of presently available clinical indices.

**Chapter 6** In this chapter, we proposed the pressure gradient at a fixed flow velocity of 30 cm/s (dP v30) as a new index for the assessment of functional stenosis severity. This index can be obtained during contrast medium-induced submaximal hyperemia, thereby circumventing both the problems regarding functional assessment during resting conditions and the need for adenosine administration.

**Chapter 7** In this study, we tested the hypothesis that HMR allows accurate identification of microvascular functional abnormalities by evaluating the association
between high or low HMR and the presence of myocardial ischemia on non-invasive stress testing.

**Chapter 8** This study evaluated the impact of the magnitude of HMR for the presence, and FFR-guided identification, of reversible myocardial ischemia on non-invasive stress testing.

**Chapter 9** In this chapter, the major findings and conclusions of this thesis are discussed in view of clinical implications of these findings. Additionally, recommendations are provided with respect to future research.
References

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