Simultaneous pressure and flow velocity measurements in diagnosis and treatment of coronary artery disease

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General Introduction
1. Coronary artery disease

Coronary artery disease is rather common and manifests itself by epicardial narrowing of the supplying arteries of the heart. Such a coronary narrowing or stenosis develops over time by the formation of atherosclerotic plaques in the intima of the vessel. Progression of this stenosis leads to a decrease of perfusion pressure in the artery behind it. Consequently, the needed increase of flow through this artery as required by an increased of oxygen demand, is limited. This hindrance manifests itself initially by symptoms during exercise when the need for oxygen-rich blood increases. With increasing coronary stenosis severity, ischemia may occur already at rest. Irreversible myocardial damage or infarction may occur, which has a profound impact on cardiac morbidity and mortality. Consequently, adequate diagnosis and treatment of coronary artery disease is mandatory to improve clinical outcome.

Coronary angiography is performed if non-invasive stress-tests suggest coronary artery disease. During this procedure, which is performed by the femoral or radial route, contrast medium is selectively injected in the right or left coronary artery allowing imaging of coronary narrowings as illustrated by Figure 1.

In the coronary angiogram of Figure 1, a significant coronary stenosis is visible with 65% reduction of vessel diameter. Coronary angiography is still used as the gold standard for diagnosis of coronary artery disease although a recent study has clearly identified the superiority of functional measurements over angiographic (61). For several reasons, angiography has shortcomings in defining the physiological significance of a stenosis. The three-dimensional structure of a stenosis is poorly represented by the two-dimensional projection of an angiogram. However, even with a well defined three-dimensional representation, the pressure drop over a stenosis would be difficult to predict because resistance to flow of the perfused myocardium downstream is unknown. Certainly, simple geometric measures like percent diameter reduction are insufficient. In the past two decades, several methods have been developed to quantify the physiological significance of coronary narrowings using hemodynamic variables such as pressure drop over and reduction of flow through the stenosis.
Figure 1: coronary angiogram of the left coronary artery: a significant stenosis is present in the left anterior descending artery (arrow).

For this thesis, we used a guide wire equipped with sensors that enable simultaneous intravascular pressure- and flow velocity measurements distal to coronary stenoses in patients with coronary artery disease (Figure 2). Coronary resistances were measured and pressure drop-flow velocity relations were estimated in order to describe hemodynamic characteristics of coronary epicardial stenoses and to assess the interaction with the distal microcirculation.

The purpose of this chapter is to provide an overview of the anatomy and physiology of the coronary circulation as to put the functional measurements in such a perspective.
2. Coronary anatomy

The heart is supplied with blood by its own vascular system, the coronary circulation (Figure 3). The left and right coronary arteries originate from the aorta distal to the coronary cusps of the aortic valve. In most cases, the left coronary artery bifurcates after approximately one centimeter into the left anterior descending artery and the left circumflex artery. These three large coronary arteries bifurcate into smaller arteries over the outer surface of the heart, the epicardium. From these arteries, vessels branch off and penetrate the heart muscle or myocardium in order to perfuse all myocardial layers. After a number of bifurcations, the arterial system connects to the capillary network, which is a dense network of small vessels (diameter ~ 5 um) that are interwoven with myocardial fibers in order to facilitate exchange of oxygen, carbon dioxide and metabolites between blood and myocardial cells. From the capillary network, the blood flows into the venous system that drains into the right atrium. A small portion of coronary blood flows back into the ventricles and atria of
the heart through Thebesian sinusoids, which are a remnant of the embryological perfusion system of the heart.

Figure 3: Circulation of the heart. The right and left coronary artery originate from the aorta distal to the cusps of the aortic valve and branch into smaller arteries. The coronary veins transport the blood from the heart muscle to the right atrium. (© Elsevier, Inc. – Netterimages.com with permission)

2.1 Resistance vessels
All arteries and arterioles possess a layer of circular smooth muscle cells that enables these vessels to adjust their diameter. These smooth muscle cells will either contract or relax in response to metabolic or hemodynamic signals. Vasoconstriction will increase vascular resistance and vasodilation will reduce it. Coronary blood flow is regulated by vasoconstriction and vasodilation of small arteries (diameter between 100 - 400 μm) and arterioles (diameter smaller than 100 μm). Because the major part of coronary arterial resistance is located in these vessels (8, 9), they are called resistance vessels.
2.2 Collateral vessels
Most coronary arteries bifurcate into smaller arteries until they connect to the capillary network. However, a number of vessels connect arteries from different cardiac territories and are referred to as collateral vessels. Under physiological circumstances these vessels do not play an important role because of an absence of pressure drop over these vessels. However, when a large coronary artery becomes obstructed or occluded, flow will increase through these collateral channels to support the tissue dependent on the recipient artery (53). When ischemia develops gradually, new collateral connections will be formed by a process called arteriogenesis (63). Effective stimulation of collateral growth is generally expected to have a beneficial effect on prognosis in patients with coronary artery disease.

3. Coronary physiology

3.1 Coronary pressure distribution
Coronary blood flow is continuously adapted to changes in cardiac metabolism and in hemodynamic circumstances. Experimental arteriolar pressure measurements have proven that these adaptations are implemented by small arteries and arterioles. Blood pressure decreases gradually in the coronary system starting at arteries of about 400 μm as is demonstrated in Figure 4. This distribution of pressure as a function of arterial diameter changes when vasodilation is induced by administration of a vasodilator like dipyridamole indicating that all arterial segments with diameters smaller than 400 μm are involved in coronary blood flow control (8, 9). The mechanism by which diameter – and thus resistance – in vascular segments changes depends on the position of the vessel in the arterial tree. The smaller arterioles that are closer to the myocytes are more sensitive to changes in myocardial oxygen need. Segments with larger diameters are more responsive to autoregulatory mechanisms.
Chapter 1

Figure 4: Effect of administration of dipyridamole on the pressure distribution of coronary vessels of different sizes in an open-chest beating cat heart experiment. Measurements were performed with a microscope and micropipettes whose motion was synchronized to the beating heart using an electromechanical micromanipulator and a stroboscope. A strong effect of dipyridamole on intravascular pressure is observed in vessels with a diameter below 400 µm (Chilian et al. Am J Physiol 1989, Am Physiol Soc, used with permission).

3.2 Metabolic flow adaptation

A single responsible mechanism for adaptation of coronary blood flow to metabolic demand has not been identified despite extensive research efforts over the past 40 years. It is now generally accepted that there is not a simple mechanism but that interaction of a large number of sub-systems results in a stable and robust control system (18). A number of well-studied mechanisms are discussed. Oxygen and carbon dioxide are logical candidate mediators given their role in gas-exchange and metabolism. The relation between coronary blood flow and coronary venous oxygen and carbon dioxide tensions as surrogates for myocardial tissue values have been studied in animals. A strong and synergistic relation between microvascular conductance and tension of oxygen and carbon dioxide was found but could explain only 40% of the increase of flow that was observed during cardiac pacing (3, 17).
Several research groups have focused on adenosine, $K_{ATP}$-channel activation and nitric oxide as pathways for metabolic flow adaptation. Stepwise blockade of these three mediators in exercising swine decreased the level of coronary venous oxygen tension (38). Moreover, the negative relationship between myocardial oxygen consumption and coronary venous oxygen tension became steeper after each step, suggesting an additive role of these pathways in metabolic flow adaptation. Despite the blockade of these pathways of vasodilation, the myocardium was not at risk of ischemia during exercise indicating that other factors play a role as well. In exercising dogs, blockade of the adenosine receptor and nitric oxide synthesis did not induce convincing changes in flow and additional blockade of $K_{ATP}$-channel activation was needed to induce a comparable effect as in exercising swine. This observation suggests a redundant mechanism in dogs with an important role for $K_{ATP}$-channel activation but in a manner different from swine implying species dependency for metabolic flow adaptation (27). However, these results could not be reproduced in a more recent study, during which a decrease of coronary venous oxygen tension appeared not to be related to myocardial oxygen consumption (62). It should be mentioned that this interpretation may not be correct since the drugs used to block nitric oxide action and $K_{ATP}$-channel activation, Nω-nitro-L-arginine and glibenclamide respectively, were administered differently, intravenously in swine and intracoronary in dogs. Therefore, systemic effects of the blocking agents may have influenced the results of the study using swine. In conclusion, adenosine, $K_{ATP}$-channel activation and nitric oxide are likely to be part of integrated pathways that influence blood flow during exercise, but are not essential for metabolic flow adaptation.

Endothelin has been proposed as a candidate mediator of metabolic flow adaptation. Being a potent vasoconstrictor, endothelin is responsible for a level of preconstriction of arteries and arterioles. It was shown that the vasodilatory effect of an endothelin antagonist decreased with increasing exercise intensity (60). Moreover, it was shown that during exercise, myocytes produce a factor that antagonizes endothelin (37) which led to the suggestion that a decrease of endothelin activity may play a role during exercise induced coronary vasodilation. Interestingly, evidence exists that $\alpha_1$-adrenergic activity plays a role in the release of endothelin. Merkus et al. observed that administration of phenylephrine, a selective $\alpha_1$-adrenergic agonist
resulted in vasoconstriction of coronary arterioles that lasted over two hours (37). This vasoconstriction was not abolished by administration of prazosin, an α-blocking agent. On the other hand, vasodilation did occur after administration of an endothelin antagonist or an endothelin-receptor blocking agent. The same group reported that endothelin is likely to be produced by the endothelial cell, stimulated by a factor that is produced by cardiac myocytes. The elimination of this effect by losartan, a selective angiotensin-II receptor antagonist, implies that angiotensin-II may be the link between the α-adrenergic system and endothelin mediated vasoconstriction (36). However, given its long lasting vasoconstrictive effect, endothelin-mediated vaso-activity is likely not rapid enough for direct adaptation of coronary blood flow to metabolic needs.

Although vaso-active effects of the autonomous nervous system have been described, its influence is not crucial for metabolic flow adaptation, which is illustrated by the fact that heart transplantation can be performed with success, despite the unavoidable denervation of the donor heart. Therefore, the rapid vasodilation that results from beta-receptor stimulation during exercise is believed to act as a feed forward mechanism (45), in order to prepare the coronary circulation for increased oxygen need.

The list of substances and mechanisms that influence metabolic flow adaptation could be much longer, but a comprehensive discussion of all mechanisms is beyond the scope of this introduction. We conclude that metabolic flow adaptation is an integrated regulatory system consisting of multiple mediators and pathways that enable the coronary circulation to match myocardial oxygen need. To a certain extent this control system enables compensation for the additional resistance to flow exerted by the epicardial stenosis. However, when the regulatory range is too much restrained, myocardial ischemia will result.

3.3 Autoregulation

Although adaptation of coronary blood flow to myocardial oxygen demand is necessary, blood flow should not change when oxygen demand is constant, regardless of changes in coronary arterial pressure. Variations in coronary pressure at constant oxygen consumption are counteracted by an intrinsic mechanism called autoregulation. Autoregulation is therefore important for understanding the
physiological impact of a stenosis on coronary perfusion because of its effect on the coronary pressure downstream.

The mechanism of autoregulation is illustrated by Figure 5 (46). In that experiment, perfusion of the coronary system was uncoupled from the performance of the left ventricle by cannulation and artificial perfusion of a major coronary artery. In this way, coronary pressure could be changed independently from aortic pressure. When coronary pressure decreases, autoregulation preserves coronary blood flow by reducing coronary resistance and vice versa and results in the so-called autoregulatory plateau. The height of that plateau depends on the level of oxygen consumption. Many mechanisms are known to play a role in autoregulation and a number of these mechanisms are also involved in metabolic flow adaptation. A control mechanism that conceptually is connected to autoregulation is the myogenic response.

Arteriolar smooth muscle continuously develops tone in response to pressure in the vessel lumen. Smooth muscle tone increases when luminal pressure increases. This myogenic response may even result in a smaller vessel diameter at higher pressure. The sensitivity of the myogenic tone to pressure has been studied in isolated vessels and it has been demonstrated that it is largest in vessels of about 90 μm in diameter (33).

However, vessels are not acting alone but in concert as dictated by the vascular network of which they form a part. Theoretical models of vascular networks based on properties measured on isolated vessels revealed that myogenic response to a change in perfusion pressure is strongest in vessels of 190 μm (11). Coronary vascular tone is not only influenced by pressure but also by flow through a vessel segment. An increase of flow through a vessel leads to an increase of shear stress on the vessel wall and this triggers a mechanism called flow-dependent dilation. Flow-dependent dilation is mediated by nitric oxide, produced by endothelial cells in response to wall shear stress exerted by the flowing blood, which then diffuses into adjacent smooth muscle cells causing vasodilation (31, 49). As with the myogenic response, flow-dependent dilation is not directly affected by metabolism of the myocytes. Still, it contributes to the control of the coronary system as a whole since it amplifies metabolic flow adaptation of the smallest arterioles by responding with dilation in response to the increased flow levels. This view is supported by an observed
stronger dilation of larger vessels in response to a flow increase (32). A comparable mechanism is called endothelium derived hyperpolarizing factor (EDHF)-mediated vasodilation. EDHF-mediated vasodilation predominantly occurs in small arteries and arterioles and is assumed to serve as a backup system in case production of nitric oxide is compromised (44). Both H$_2$O$_2$ and epoxyeicosatrienoic acid are assumed to act as EDHF although several other substances are known have hyperpolarizing properties too (19).

Vasodilation of arterioles can be achieved by administration of a vasodilating drug such as adenosine. During this so-called hyperemic state control of vascular tone is eliminated and microvessels behave like passive elastic tubes (32). During hyperemia, the relation between coronary pressure and flow approximates a straight line above a certain pressure as is demonstrated in Figure 5. Pharmacological induction of hyperemia is used to study the difference between passive vascular behavior and control conditions, for example to estimate vascular reserve. This topic is further discussed in section 4.

**Figure 5:** Autoregulation as demonstrated by maintenance of coronary blood flow at steady levels despite increasing perfusion pressure. Decrease of myocardial oxygen consumption leads to a decrease of blood flow. The dashed line through the triangles represents the passive pressure-flow relation during maximal vasodilation (Mosher et al. Circ Res 1964, with permission).
3.4 Interaction of Metabolic Flow Adaptation and Autoregulation

Autoregulation and metabolic flow adaptation are strongly interrelated. One may argue that practically each mechanism that has been discussed above plays a role in both manifestations. A change in resistance in a certain vascular segment changes flow and pressure in adjacent segments and may alter the metabolic state of the myocytes dependent on that segment. For example, an increase of oxygen demand causes the smallest resistance vessels to react with a dilatory response through metabolic flow adaptation. This will initially result in a decrease of vascular pressure and therefore a decrease of myogenic tone. In order to facilitate the concurrent increase of flow, larger upstream arterioles dilate as a result of flow-dependent dilation, until all vascular diameters are adapted to the new situation (28).

3.5 Effect of myocardial contraction on flow

The contraction of the myocardium during systole not only expels blood from the ventricles but also exerts compressive forces on the intramural coronary vessels. Scaramucci already observed in 1689 that this results in a pulsatile coronary flow pattern with maximum arterial flow during diastole and squeezing of intramural vessels during systole, resulting in augmented venous outflow. In 1981 Spaan et al. proposed the intramyocardial pump model to explain the asynchronous flow patterns of arteries and veins (59). The asynchronous in- and outflow of blood to and from the coronary microcirculation during the cardiac cycle implies that the amount of blood in the myocardium is smaller during systole than during diastole (Figure 6). This variation of blood volume is possible because of the elasticity of the microvascular walls resulting in what is denoted as intramyocardial compliance. Because intravascular blood volume is lower during systole, luminal vascular diameter is smaller. Hence, systolic resistance of intramural vessels may assumed to be higher than diastolic resistance. It is important to note that volume variations are not instantaneous and systole and diastole are not long enough to allow for a steady state in volume and resistance to be established within a cardiac cycle.
3.6 Subendocardial and Subepicardial Flow Differences

Myocardial blood flow is not distributed homogeneously in the walls of the left ventricle. In fact, flow through the subendocardial layers of cardiac muscle depends highly on perfusion pressure and is hindered more by cardiac contraction than subepicardial flow (5). This hindrance of subendocardial flow is caused by a much higher subendocardial tissue pressure compared to subepicardial tissue pressure. Although tissue pressure is difficult to measure, virtually all animal-experiments on this subject documented a gradient of tissue pressure across the myocardium (42, 47). At the subendocardial level, tissue pressure is close to left ventricular pressure, while at the subepicardial level tissue pressure approaches intra-thoracic pressure. Because high tissue pressure hampers coronary blood flow, this implies that the subendocardium is at increased risk of hypoperfusion especially when coronary perfusion pressure is decreased. Indeed, when coronary perfusion pressure was decreased in awake dogs, subendocardial blood flow decreased at higher perfusion pressures than subepicardial blood flow which resulted in subendocardial stunning while the subepicardium was still functional (5). This explains the increased vulnerability of the subendocardium to ischemia or infarction when exposed to decreased perfusion pressure (e.g. in case of shock or coronary stenosis) (35).
3.7 Diastolic time fraction

The duration of diastole relative to that of the complete heart cycle, or diastolic time fraction (DTF), is a determinant of coronary blood flow. However, DTF is especially related to subendocardial perfusion as was demonstrated by open chest dog heart experiments (1). Radioactive labeled microspheres were injected at different heart rates with and without administration of adenosine. DTF decreased when heart rate increased. More importantly, the decrease of DTF was associated with a decrease of subendocardial blood flow during hyperemia, whereas subepicardial conductance did not change significantly. Nevertheless, in the absence of a coronary stenosis, subendocardial blood flow reserve was sufficient to meet metabolic demand although it decreased to a third of the resting value during tachycardia. A similar study on goat hearts using fluorescently labeled microspheres revealed that a decrease in perfusion pressure caused an enhanced dependency of subendocardial perfusion on DTF (21). This implies that during exercise the subendocardium is at increased risk of ischemia when perfusion pressure is decreased due to coronary stenosis, especially during tachycardia. Interestingly, there is evidence that the heart has developed a protective mechanism against subendocardial ischemia. In exercising humans with coronary artery disease, the ratio of diastolic time to systolic time per minute is closely related to stenosis severity at the threshold of myocardial ischemia (20). Furthermore, when perfusion pressure is decreased, DTF increases in anaesthetized dogs (39).

4. Coronary pathophysiology

The previous section discussed determinants of myocardial perfusion mainly on a microvascular level. Coronary stenoses were referred to as a cause of diminished perfusion. A considerable part of this thesis is about coronary stenoses, determination of their functional severity and factors that influence their significance. For a better understanding of these topics, discussion of some basic principles of fluid- and stenosis dynamics is necessary.
4.1 Basic fluid- and stenosis dynamics

Fluid tends to flow in a laminar pattern through a tube at moderate velocities characterized by a parabolic velocity profile (Figure 7). In such profile flow velocity increases from zero at the vessel wall to a maximum value in the center of the vessel lumen. Average flow velocity, \( v \), equals half maximum flow velocity. Therefore, volumetric blood flow, \( Q \), can be calculated as:

\[
Q = A \cdot v = \pi \cdot r^2 \cdot v
\]

where \( A \) equals vessel cross-sectional area and \( r \) equals vessel radius. The frictional energy losses result in a loss of pressure, \( \Delta P \), over a vessel segment according to the law of Poiseuille:

\[
\Delta P = \frac{128 \mu L}{\pi D^4} Q
\]

where \( \mu \) is viscosity of the fluid, \( L \) is the segment length and \( D \) is vessel diameter. Equation 2 demonstrates that vessel diameter is a stronger determinant of pressure loss than vessel length. Note that according to the law of Poiseuille the relation between pressure loss and flow is linear.

When flow velocity exceeds a certain value, disturbances of the laminar flow pattern may propagate and result in a turbulent flow pattern. Turbulence implies eddy-like chaotic motion of fluid and in any case the gradual increase of velocity towards the vessel center has disappeared. Turbulent flow is associated with increased shear stresses, especially at the vessel wall and as a result the pressure drop over a tube exceeds that of laminar flow at the same volume flow. The occurrence of turbulent flow can be predicted by the Reynolds number, \( R_e \):

\[
R_e = \frac{\rho v D}{\mu}
\]

where \( \rho \) is the density of the fluid. Usually, turbulent flow begins to develop above Reynolds numbers of 2100 and when the Reynolds number exceeds 4000, the entire flow field becomes turbulent. However, these values may be influenced by the state
General Introduction

of the vessel, e.g. roughness of the vessel wall (due to atherosclerosis), curvature and bifurcations. In general, flow is laminar in all healthy vessels of the human body, except for the ascending aorta and the proximal pulmonary artery during peak systole.

Figure 7: Blood flow velocity increases in a parabolic fashion from vessel wall to the center of the lumen when observed far enough from the entrance of the vessel (about 10 times the diameter). The parabolic fashion results in minimal frictional energy losses.

When the lumen diameter of a vessel decreases due to a stenosis, pressure drop will not only increase as a result of the law of Poiseuille. A second mechanism of pressure loss over a stenosis exists that was first described by Bernoulli. Blood flow velocity needs to increase at the entrance of a stenosis because volume flow is constant (see Figure 8). Consequently, kinetic energy of the blood increases at the cost of potential energy. This results in a decrease of pressure, which can be understood as a potential energy density, inside the stenosis, which has clinical relevance as will be discussed later. In principle potential energy can be recovered when the blood decelerates again when leaving the stenosis. However, blood enters the vessel distal of a stenosis with a relatively high velocity in the shape of a jet, which causes flow separation and recirculation with eddies. This generates heat which dissipates to the surrounding tissues at the cost of potential energy recovery. Therefore, the loss of energy induced by the stenosis are referred to as exit loss.

Exit-losses ($\Delta P_e$) are added to viscous losses ($\Delta P_v$) to calculate total pressure loss induced by a stenosis:

$$\Delta P = \Delta P_v + \Delta P_e = A \cdot Q + B \cdot Q^2$$  \hspace{1cm} \text{Eq. 4}

where $A$ and $B$ are related to geometrical factors of the stenosis and to viscosity and density of blood. $A$ and $B$ are constant for a given stenosis geometry. Note that exit losses are related to the square of flow, which results in a quadratic relation between
flow through the stenosis and pressure drop over the stenosis. Resistance to flow is by definition equal to the pressure drop over the stenosis divided by flow, which results in the following equation:

\[ R = A + B \cdot Q \]  \hspace{1cm} \text{Eq. 5}

where \( R \) is stenosis resistance. Hence, stenosis resistance has a constant viscous component and a flow dependent component that results from exit losses. It is important to note that stenosis resistance is not constant. Stenoses of clinical importance are mostly eccentric. This implies that part of the vessel wall inside the stenosis is not necessarily atherosclerotic and rigid, but may be flexible and deformable. When intraluminal pressure inside the stenosis decreases as a result of increased flow velocity, this may cause the flexible part of the wall of the stenosis to deform in the direction of the stenosis lumen. When this happens, the stenosis may partially collapse and further impede flow and inevitably contributes to myocardial ischemia (56). This phenomenon may occur especially during exercise when flow velocity is increased and therefore dynamic pressure loss inside the stenosis is higher.

In conclusion, blood flow in a stenosed vessel is hampered by increased viscous and exit losses. The resistance of a stenosis increases with flow. In some cases, an eccentric stenosis may collapse when flow exceeds a critical level, causing a change of geometry accompanied by an increase of resistance.

Figure 8: At the entrance of the stenosis acceleration occurs at the cost of blood pressure inside the stenosis. Blood exits the stenosis in the shape of a jet stream. The subsequent deceleration of blood is accompanied with flow separation and formation of eddies, which generate heat, at the cost of blood pressure distal to the stenosis.
4.2 Evaluation of stenosis severity during cardiac catheterization

As discussed above, coronary angiography is not optimal for detection of significant stenoses. Often, a coronary artery stenosis is treated when lumen diameter is reduced by 70%. Nevertheless, it is well established that coronary lesions with a diameter reduction between 25% and 70% can cause ischemia during exercise (66). This discrepancy has led to the development of guide wires for use during PCI that are equipped with sensors for intracoronary measurement of Doppler flow velocity or pressure. With these hemodynamic variables, functional diagnostic parameters can be obtained to assess the hemodynamic significance of a coronary artery stenosis during catheterization. A number of these parameters are discussed below.

Figure 9: Drop of flow through a stenosis as function of diameter reduction of a coronary vessel. Broken line: with tone intact this basal flow is only affected when the diameter reduction is above 80% because of autoregulatory compensation downstream. Solid line: maximal blood flow resulting from temporary occlusion or administration of contrast fluid. Maximal flow level is affected when vascular diameter is reduced by 30%. For higher stenosis degrees the decrease of maximal flow is more pronounced. The ratio between maximal flow and basal flow at the same stenosis is defined as flow reserve which has proven to be a sensitive descriptor of functional stenosis severity (Gould and Lipscomb, Am J Cardiol 1974, with permission).
4.2.1 Coronary flow reserve

In 1974 animal experiments demonstrated that coronary blood flow would increase temporarily after short occlusion of the vessel or after intracoronary administration of contrast fluid (22, 23). This reactive hyperemic response was attenuated in the presence of an artificially induced stenosis. The ratio of hyperemic to resting blood flow was denoted as coronary flow reserve and decreased when the coronary stenosis caused a diameter reduction of 30% or more (Figure 9). Resting blood flow was not affected until arterial diameter was reduced by more than 85%. This observation explained why coronary stenoses, appearing to be mild on coronary angiography could still be associated with chest pain during exercise or stress (see also Sections 3.1 and 3.2). Hyperemia proved to be more pronounced when it was pharmacologically induced by papaverine or adenosine (10, 65, 67).

Assessment of coronary flow reserve of individual arteries in patients with coronary atherosclerosis was hampered due to the technical difficulty to measure coronary flow (34). Fortunately, in 1992 a new guide wire equipped with a Doppler transducer at the tip became available for use during coronary angioplasty (16). Measurements of flow velocity were validated against absolute flow measurements in vitro. In patients with coronary atherosclerosis, coronary flow velocity reserve (CFVR) distal to the stenosis was considerably lower than in an adjacent unaffected coronary artery (48). After treatment CFVR increased to a value close to that of the healthy artery. CFVR distal to an intermediate coronary stenoses became an established diagnostic tool that correlated well with reversible perfusion defects as assessed by myocardial perfusion scintigraphy (7, 24, 29, 43, 64). The consensus is that a value below 2.0 indicates a significant stenosis that needs treatment (30).

Despite the success of CFVR, a number of pitfalls have been recognized since its introduction (25). First, flow velocity depends on vessel diameter and therefore arterial smooth muscle tone needs to be minimized by administration of a large vessel vasodilator like nitroglycerin before measurement. Second, both baseline and hyperemic flow are influenced by physiological factors. Baseline flow velocity depends on the oxygen consumption of the myocardium, which implies that every parameter that increases oxygen need will lead to an increase of resting flow velocity (e.g. tachycardia, positive inotropic agents, hypertrophy). A decrease of oxygen
content of the blood may also increase resting blood flow (e.g. anemia, hypoxemia). Clinical data confirmed that hyperemic flow velocity is influenced by e.g. heart rate, blood pressure and contractility (13, 54). Nevertheless, CFVR is a valuable addition to the diagnostic toolkit of the interventional cardiologist as long as abovementioned issues are regarded during clinical decision making.

4.2.2 Fractional flow reserve

Shortly after introduction of the guide wire that was equipped with a Doppler crystal, a new guide wire was presented that enabled measurement of intracoronary pressure distal to a stenosis (14). This guide wire was used to measure a pressure based derivation of the hyperemic flow distal to a stenosis \(Q_d\) as a fraction of the hyperemic flow that would be possible in the same vessel without a stenosis \(Q_N\). The derived flow ratio was termed myocardial fractional flow reserve (FFR\(_{myo}\)) and is usually calculated by division of pressure distal to the stenosis \(P_d\) by aortic pressure \(P_a\) during hyperemia (52):

\[
FFR_{myo} = \frac{Q_d}{Q_N} = \frac{P_d}{P_a}
\]

Eq. 6

The model based FFR\(_{myo}\) can be derived from flow as follows (58):

\[
FFR_{myo} = \frac{Q_d}{Q_N} = \frac{P_d - P_v}{HMR_S} = \frac{P_d - P_v}{P_a - P_v} \cdot \frac{HMR_N}{HMR_S}
\]

Eq. 7

Where \(P_v\) is hyperemic venous pressure. HMR\(_S\) and HMR\(_N\) are hyperemic coronary microvascular resistances distal to the stenosis or distal to the healthy artery respectively. A vital assumption in the theory of FFR\(_{myo}\) is that hyperemic coronary microvascular resistance is assumed constant regardless of perfusion pressure so that HMR\(_S\) and HMR\(_N\) can be eliminated from the equation. In the clinical setting, venous pressure is often neglected because its measurement requires additional catheterization of the right atrium.
Chapter 1

An advantage of the use of $\text{FFR}_{\text{myo}}$ for estimation of stenosis severity over CFVR is that baseline values of pressure or flow do not influence its value. Therefore, reproducibility of $\text{FFR}_{\text{myo}}$ is better and (13). When measured in the presence of a stenosis, $\text{FFR}_{\text{myo}}$ values below 0.8 proved to correlate well to ischemia as documented by exercise testing, thallium scintigraphy or stress echocardiography (2, 7, 12, 50, 51). Moreover, coronary pressure proved to be easier to measure than vlocity, which resulted in an increasing popularity of $\text{FFR}_{\text{myo}}$ as a diagnostic tool to determine the clinical significance of intermediate coronary lesions among clinicians.

An important point of concern with respect to $\text{FFR}_{\text{myo}}$ is its dependence on hyperemic coronary microvascular resistance (HMR) (52, 57). In order to enable derivation of fractional flow from pressure measurements it was assumed that HMR is minimal and constant during maximal vasodilation. However, in patients with multivessel disease, hyperemic microvascular resistance correlates with the severity of the coronary stenosis (6). Moreover, when results of $\text{FFR}_{\text{myo}}$ and CFVR were compared, patients with discordant results (non-diagnostic $\text{FFR}_{\text{myo}}$ and significantly decreased CFVR or vice versa) had either increased or decreased HMR, which is in line with abovementioned parametric analysis (40). This implies that $\text{FFR}_{\text{myo}}$ may underestimate true functional stenosis severity when HMR is increased.

4.2.3 Hyperemic Coronary Stenosis Resistance

Already in 1979 it was recognized that the functional significance of a coronary stenosis would best be described by its resistance to flow (68). Although feasible in animal experiments, measurements of coronary stenosis resistance was hampered in patients due to technical difficulties. Meuwissen et al. used separate velocity and pressure wires to measure pressure and flow velocity serially in order to be able to calculate hyperemic coronary stenosis resistance (HSR) in patients with coronary artery disease. HSR was compared to myocardial perfusion scintigraphy (41) and proved to predict ischemia better than either CFVR or $\text{FFR}_{\text{myo}}$.

HSR needs further validation in order to determine its reliability in patients with coronary artery disease. For example, the behavior of HSR in response to variations in heart rate or blood pressure should be studied in order to determine its reproducibility. Moreover, a large study with follow-up is necessary to determine the prognostic power of HSR.
4.2.4 Hyperemic Coronary Microvascular Resistance

Hyperemic coronary microvascular resistance plays an important role in determining the physiological significance of a coronary stenosis: both CFVR and FFR_{myo} are influenced by its magnitude. However, apart from its role in the physiological assessment of stenosis severity, it is to be expected that coronary microvascular resistance by itself will prove to be an important clinical variable. Evidence mounts that diseases like diabetes mellitus and hypertensive cardiomyopathy are associated with increased coronary microvascular resistance (4). Measurement of microvascular resistance may very well aid the clinician in assessment of microvascular dysfunction. Calculation of microvascular resistance from pressure and flow velocity measurements has been the subject of discussion for a long time because there is no linear relation between the two variables. When coronary pressure decreases, coronary flow ceases before pressure reaches zero, which is to be expected with a linear relationship. The intercept pressure was denoted as ‘zero flow pressure’ and several studies indicated that this pressure is above right atrial pressure. The cause of the non-linear nature of pressure-flow line can be found in the analysis provided above on the effects of distensibility of intramural vessels and the compression of these vessels by contraction of the heart as recently has been reviewed (26). However, these non-linear characteristics are ignored by others and the non-zero intercept explained by collateral flow exclusively which implies denial of the overwhelming evidence of the biophysical mechanisms involved in coronary hemodynamics.

In this thesis no solution to the discussion on determinants of hyperemic coronary microvascular resistance is provided. However, the relevance of the difference of opinion is assessed for different degrees of stenosis severity.

4.2.5 Stenosis Pressure Drop-Flow Velocity Relationships

The relation between pressure gradient across a coronary stenosis and flow velocity provides a comprehensive picture of the hemodynamic behavior of the stenosis regardless of the level of hyperemia that is obtained. These relationships also enable recognition of collapsible stenoses with changing pressure drop-flow velocity relations (56), that would otherwise go unnoticed. These relations were shown in 25% of an a-selective group of patients (15, 55). Incorporation of such a diagnostic
modality would require an on-line representation of these relationships which is at present not the case.

5. Aims and outline of this Thesis

The general aim of this thesis was to study hemodynamics of the coronary circulation in patients with coronary artery disease by simultaneous intracoronary measurements of coronary pressure and Doppler blood flow velocity distal to a coronary stenosis using a novel dual-sensor guide wire for percutaneous coronary intervention. In the present chapter (chapter 1) a background for this thesis was provided.

Chapter 2 presents the first measurements using the ‘Combowire’. The hypothesis was tested that evaluation of stenosis hemodynamics is performed more comprehensively when distal coronary pressure and flow velocity are measured simultaneously. Measurements were performed before and after treatment steps in order to study the effect of percutaneous coronary intervention on stenosis resistance and on pressure gradient-flow velocity relations.

In chapter 3 we studied the effect of pressure restoration after stepwise-executed percutaneous coronary intervention on coronary microvascular resistance. Simultaneous coronary pressure and flow velocity measurements were performed throughout the treatment procedure in order to study changes in microvascular resistance and possible underlying mechanisms.

In chapter 4 hyperemic coronary microvascular resistance was calculated with and without a correction for collateral flow. In a wide range of FFR-values, the difference between both calculations of HMR was estimated. The hypothesis was tested that correction for collateral flow does not importantly affect HMR.

In chapter 5 we studied the effects of hemodynamic challenges on coronary physiological parameters. Measurements of pressure and flow velocity were performed distal to stenoses of variable severity before and during cardiac pacing (at 120 BPM) and during elevation of blood pressure (by 30 mm Hg) by phenylephrine infusion. Established intracoronary diagnostic parameters were studied during these circumstances and their behavior was explained on the basis of induced changes in coronary resistances and pressure gradient-flow velocity curves.
In chapter 6, measurements of pressure and flow velocity were performed after coronary stenting of significant atherosclerotic lesions. Measurements were repeated after intracoronary administration of urapidil, a selective $\alpha_1$-receptor blocking agent with vasodilatory properties. Measurements were separated in systolic and diastolic parts and diastolic time fraction was calculated to test the hypothesis that urapidil has beneficial effects on coronary perfusion after stenting.

In chapter 7, the results and conclusions of abovementioned chapters are discussed and put into broader perspective. General conclusions are drawn and recommendations are made for future research.

References

Chapter 1


