Chapter 8

General discussion and future outlook
In this thesis we investigated the human coronary circulation based on combined intracoronary pressure and flow velocity measurements obtained by dual-sensor guidewires. Functional indices of coronary stenosis severity derived from these measurements, such as fractional flow reserve and coronary flow velocity reserve, are routinely used in the catheterization laboratory for clinical decision-making [8]. The currently used clinical indices are based on the per-beat mean values of pressure and/or flow velocity and do not utilize information derived from the time-dependent nature of these pulsatile signals. As outlined in the introduction and background (Chapters 1 and 2), recent technological advances allow simultaneous acquisition of high-fidelity coronary pressure and velocity waveforms, which presents new possibilities for improving our understanding of the influence of vascular pathologies on myocardial perfusion.

Chapters 3-5 explored different approaches of phasic signal analysis that may ultimately lead to new clinical indices for the assessment of epicardial and microcirculatory disease. The analysis of both signal energy and wave intensity was introduced to gain mechanistic insight about coronary-myocardial interaction in healthy and diseased vessels. Chapters 6 and 7 focused on the influence of cardiac contraction on coronary perfusion, with special interest on the role of the Diastolic Time Fraction (DTF). Chapter 6 describes the contribution of an increase in DTF to the beneficial effect of alpha-receptor blockade after percutaneous coronary intervention. Chapter 7 is a theoretical study predicting the distribution of perfusion over the different myocardial layers as a function of DTF and perfusion pressure.

Our major findings and conclusions are discussed below, separated by relevant clinical and physiological topics.

**Determinants of pulsatility in coronary blood flow**

Coronary blood flow is pulsatile, but the mechanistic determinants are still unclear. Current theories explaining pulsatility in coronary blood flow are mostly based on results from animal studies that employed coronary perfusion systems. In such an experimental setup, pressure or flow can be maintained constant during the cardiac cycle and the effect of cardiac contraction is investigated by the variations in the uncontrolled signal. Such an approach is not feasible in the catheterization laboratory and a technique had to be developed to analyse the pulsations in pressure and flow velocity without the need to keep one of the two constant.

Based on the concept of signal energy we introduced indices to describe the pulsatile content of pressure and flow velocity. It may be assumed that when coronary pressure is kept constant, as is possible in animal experiments, the pulsatile velocity index (Pvl) depends on myocardial contraction in the same way as the amplitude of coronary blood flow. A similar assumption holds for the relation between the pulsatile pressure index (PPI) and the amplitude of pressure pulsations under conditions of constant flow perfusion.

We found that the pulsatility of coronary flow velocity depended on microvascular conductance (Chapter 3), which supports the intramyocardial pump model, according to which the systolic-diastolic variations in coronary blood flow are attributed to the corresponding changes in intramural intravascular volume and are impeded by the coronary resistance vessels. However, there is still a dispute with
respect to the cause of these intramural volume variations. On the one hand there is evidence that left ventricular pressure, especially in the early and late phase of systole, is responsible [12], while on the other hand there are also theories that define the cause for these volume variations on the basis of the time-varying elastance concept [9, 10]. According to this concept changes in the stiffness of the cardiac muscle cause the intramural vascular volume changes. However, support for this hypothesis stems from experiments where flow variations were related to coronary perfusion pressure. Using Pvi as an index for flow variations, we could not confirm a relationship between flow variations and coronary pressure. Hence, our findings based on signal energy analysis do not support the elastance concept.

We also found discrepancy with the elastance concept from our study on coronary Wave Intensity Analysis (WIA), as described in Chapter 5. The flow-limiting effect of cardiac contraction was identifiable by a backward compression wave which was consistently found in early systole, when elastance is still low and left ventricular pressure has a large influence on myocardial tissue pressure. This observation is at odds with the elastance concept, since the largest effect on coronary blood flow occurs when elastance is still rather low. Also the fact that no backward waves are generated in mid-systole, when elastance is maximal, suggests that a dominant direct effect of elastance on coronary blood flow pulsatility is unlikely.

**Pulsatile stenosis resistance index**

The indices currently used in clinical practice for the assessment of the physiological significance of a coronary stenosis are based on the per-beat averages of pressure and/or flow velocity and require drug-induced vasodilation of the microvascular resistance vessels [8]. A practical problem when using sensor-tipped guidewires is the stability of the pressure transducer, which frequently results in drift of the pressure signal, thereby introducing uncertainty in the determination of the pressure-related indices. An index of functional stenosis severity that does not require pharmacological vasodilation and is not sensitive to drift of the pressure signal has therefore great potential.

From the pulsatile energy-based indices for aortic pressure and distal coronary pressure and flow velocity we derived a pulsatile resistance index (PRI) for the stenosis. We found that PRI at rest correlated remarkably well with the mean stenosis resistance determined at maximal vasodilation. Notably, a different relation was found for left and right coronary arteries. We believe that this difference derives from the influence of myocardial contraction on the distal coronary pressure waves. Since right ventricular pressure is much lower than in the left ventricular chamber, the stenosis-induced resistance to pulsatile flow variations was lower in right compared to left coronary arteries.

PRI at rest demonstrated an excellent correlation with mean stenosis resistance at hyperemia, which in turn has an excellent predictive value for inducible ischemia as determined by SPECT [11]. Because its determination circumvents practical problems associated with achievement of maximal vasodilation and drift in the pressure sensor, this pulsatile resistance index represents a promising new parameter for the clinical decision-making.
Pressure-dependence of hyperemic coronary microvascular resistance

Both animal and clinical studies have convincingly demonstrated that microvascular resistance at hyperemia depends on arterial distending pressure [6, 14]. The physical explanation of this phenomenon is simply related to the elasticity of the passive vessel wall. An increase in luminal pressure will distend vessels with relaxed smooth muscle tone and thereby decrease their flow resistance proportional to the fourth power of the increase in vessel diameter. A recent clinical study [1] has challenged this straightforward physical principle of a pressure-dependent microvascular resistance, based on simplifying assumptions regarding the interpretation of coronary pressure-flow lines [13].

The debate with respect to the pressure-dependence of minimal coronary microvascular resistance could be examined in a different context by studying coronary Wave Intensity (WI). In Chapter 5 we employed coronary WI analysis as a tool for assessing the coronary microcirculation. It was shown that the energy carried by backward-travelling waves increases when microvascular conductance is augmented by distal vasodilation. Similarly, we found an increase in the energy carried by the hyperemic backward waves after stent placement. Consequently, this effect of revascularization can also be attributed to an improved conductance of the coronary microcirculation. Since distal coronary perfusion pressure is restored after the removal of the stenosis, we postulate that our findings are in agreement with a pressure-dependent hyperemic microvascular resistance.

Wave speed

Wave speed is an important physiological parameter because of its relation to vessel wall distensibility, but it is also a fundamental parameter needed by WIA to separate waves into their forward and backward components. Due to their unique anatomy, the coronary arteries introduce difficulties to all commonly used invasive and non-invasive techniques to assess pulse wave velocity. A recent study presented a promising new method to derive local coronary wave speed in humans [4]. This single-point technique yielded satisfactory results in healthy coronary arteries at resting flow conditions, but its applicability had not yet been tested in diseased coronary vessels or after vasodilation of the downstream vascular bed. Focal coronary obstructions may generate localised reflection sites that affect the accuracy of this method.

These considerations prompted the study presented in Chapter 4, where we applied the single-point technique to pressure and velocity measurements obtained in diseased coronary vessels before and after revascularization. It was found that wave speed was linked to distal coronary microvascular resistance, limiting its accuracy to reflect local vessel wall properties. However, the shape and timing of separated WI contours were not very sensitive to relatively large deviations of wave speed from its calculated value. Consequently, despite the fact that this method may not yield true wave speed in diseased coronary vessels, our results suggest that it is still applicable for wave separation in WI analysis (Chapter 5).

Improvement of subendocardial perfusion with α-receptor blockade

The beneficial effect of α-receptor blockade after percutaneous coronary intervention (PCI) is well-established in the literature and it is generally attributed to relief of diffuse coronary vasoconstriction [5, 7]. The possibility of a change in the...
cardiac contractile pattern as an explanation for this effect has not been investigated before. The results presented in Chapter 6 demonstrate that diastolic duration was prolonged by α-receptor blockade after PCI, irrespective of heart rate. Animal studies have provided evidence that an increase in the diastolic time fraction enhances especially subendocardial perfusion. This mechanism, which could be mediated by direct action on myocardial α₁-adrenergic receptors, therefore may represent a possible adjunctive effect of α-receptor blockade after PCI benefitting subendocardial perfusion in patients.

Indices of functional stenosis severity and subendocardial perfusion

The model study presented in Chapter 7 further highlights the importance of diastolic time fraction for subendocardial perfusion. The model predictions illustrate how the interplay of DTF and perfusion pressure during maximal hyperemia can alter the distribution of perfusion in different layers of the myocardial wall, leading to epicardial steal at the expense of endocardial flow.

These findings have bearing on functional tests in the catheterization laboratory where the physiological significance of a stenosis is determined during pharmacologically induced vasodilation. The model predictions indicate that hemodynamic measurements performed during adenosine-induced hyperemia may overestimate the subendocardial perfusion during physical exercise, when heart rate is elevated and therefore DTF is reduced. As a consequence, ischemic thresholds of functional stenosis severity derived from epicardial hemodynamic measurements should take into account DTF and coronary pressure as determining factors for coronary perfusion distribution.

Future Outlook

The research carried out for this thesis was motivated by the goal to learn more about the mechanics of coronary blood flow by "looking beyond means" and examining the pulsatile nature of pressure and flow velocity waveforms in healthy and diseased coronary arteries in humans.

Arterial waves have in the past decades predominantly been considered in the classical impedance analysis as the superposition of harmonic waves with different magnitudes and phase shifts. The underlying frequency-domain analysis makes it impossible to maintain a temporal relation between events occurring at a specific time in the cardiac cycle and the resulting frequency spectrum. In contrast, wave intensity analysis is carried out in the time domain, which facilitates interpretation of the resulting waves with respect to timing of events during the cardiac cycle [2].

Although the new techniques introduced in this thesis for the analysis of the phasic content of these coronary hemodynamic signals achieved promising results, they currently require off-line processing. A number of steps need to be taken before these methods can be applied in catheterization laboratories in daily clinical practice. Software has to be developed to allow immediate and online calculation of pulsatile energy and wave intensity. Moreover, clinical studies in a larger patient population are warranted in order to confirm the results presented in this thesis and to establish cut-off values separating physiological and pathological conditions.
The coronary microcirculation represents an increasingly important research area, since microcirculatory dysfunction is a marker of several risk factors and contributes to the pathogenesis of myocardial ischemia even in the absence of epicardial vessel disease [3]. In order to evaluate the effectiveness of novel pharmacologic or subcellular treatment modalities, an integrative hemodynamic framework is required.

In this context, WI analysis yielded promising results in its first application in diseased human coronary arteries reported in this thesis and it is worth exploring its full potential to provide a “window” to investigate the coronary microcirculation in humans from an accessible site remote from where the waves are initiated.

References


