Analysis of pulsatile coronary pressure and flow velocity: looking beyond means

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Pulsatility in coronary blood flow results from the combined action of pulsatile aortic pressure and the compression/relaxation exerted by the beating heart on the intramural coronary vessels that penetrate the heart muscle. In addition, the pattern of coronary blood flow and pressure is strongly influenced by the presence of an atherosclerotic narrowing and the vasodilatory status of the coronary microcirculation. Although recent technological advances have made high-fidelity acquisition of phasic intracoronary pressure and flow velocity possible in humans, clinical assessment of coronary artery disease and microvascular function is traditionally limited to the analysis of beat-averaged hemodynamic data.

We hypothesized that information on the condition of the coronary vessels and cardiac-coronary interaction can be extracted from the pulsatile characteristics of coronary blood flow and pressure. In this thesis we developed and applied various analysis techniques with the aim to investigate the mechanisms underlying the pulsatile nature of pressure and flow velocity in healthy and diseased coronary vessels in humans.

The first and second chapters provide a general introduction and a comprehensive review of physiological concepts relevant for coronary and stenosis hemodynamics. Chapter 2 concludes with a description of wave propagation in arteries and its assessment in the frequency and time domain. In particular, wave intensity analysis (WIA) has recently been explored as a promising time domain-based method to investigate cardiac-coronary interaction. The analytical background and in vivo applications of this method in systemic vessels are further described in the Appendix.

The clinical studies presented Chapters 3-6 of this thesis are based on simultaneous intracoronary pressure and flow velocity measurements obtained in patients undergoing treatment of a coronary artery stenosis with balloon angioplasty and stent placement. Hemodynamic signals were acquired using a 0.3-mm guidewire equipped with both a pressure and a flow velocity sensor. Data were collected at resting flow and during maximal flow after adenosine-induced coronary vasodilation in normal epicardial arteries and in diseased vessels before and after revascularization. The findings from data obtained in these patient groups are summarized below.

In Chapter 3, we investigated determinants of coronary blood flow pulsations in the context of cardiac-coronary interaction. Indices for strength of pressure and velocity pulsations were established based on the classical concept of signal energy. We demonstrated that the pulsatile energy in coronary blood flow velocity depends on microvascular conductance, thus supporting the concept of the intramyocardial pump model. According to this model, systolic-diastolic variations in coronary blood flow are caused by corresponding changes in intravascular intramural volume, which in turn are induced by heart muscle contraction/relaxation. On the other hand, flow velocity pulsations were not related to prevailing coronary pressure, thereby refuting one of the observations on which the elastance model is built, another well-accepted theory explaining cardiac-coronary interaction.

Based on these pulsatile pressure and velocity indices, we also defined an index representing the pulsatile component of stenosis resistance, PRI. We demonstrated that PRI obtained at baseline flow correlated strongly with the beat-averaged
hyperemic stenosis resistance, a clinically validated predictor of reversible ischemia. This is an important clinical finding, because the new dynamic stenosis index does not depend on pressure sensor-related drift, a common problem in clinical measurements conducted with sensor-equipped guidewires. Furthermore, the use of PRI may obviate the need for pharmacologically induced microvascular vasodilation, a recognized source of variability in the clinical assessment of functional stenosis severity.

Pulse wave velocity is an important physiological parameter due to its relation to vessel wall distensibility. The peculiar anatomy of the coronary circulation has in the past prevented wave speed determination in epicardial arteries. In Chapter 4, we investigated the applicability of a newly developed technique to assess wave speed in human coronary arteries. The technique utilizes instantaneous changes of pressure and velocity measured simultaneously at a single location and integrated over complete cycles. We found that the index of local wave speed derived from this single-point technique was paradoxically influenced by distal microvascular resistance and by the presence of a stenosis. Our findings therefore challenge the applicability of this parameter for studying local coronary vessel wall properties in conditions commonly encountered in clinical practice. In spite of this shortcoming, we showed that the single-point parameter is still useful to separate forward and backward traveling waves in wave intensity analysis, which we found to be relatively insensitive to variations in wave speed.

Wave intensity analysis, WIA, is a time-domain method that interprets incremental changes in pressure and velocity signals as the local sum of energies carried by incident forward and backward traveling waves. It is uniquely suited to study the coronary circulation as it distinguishes between forward waves generated by the variations in aortic pressure and backward waves arising from the microcirculation during cardiac contraction and relaxation. In Chapter 5, we applied WIA to study the effect of alterations in stenosis and microvascular resistance on aortic and microcirculatory contributions to locally measured coronary waves. We found that vasodilation markedly augmented the waves. Revascularization of the stenosis further increased the energy of the waves originating from the microcirculation, which are associated with the acceleration and deceleration of coronary blood flow in diastole. The increase in the size of these backward waves was related to a concomitant increase in hyperemic microvascular conductance after the restoration of coronary perfusion pressure by stenosis removal. This finding is in agreement with the notion of a pressure-dependent minimal coronary microvascular resistance, a concept that is corroborated by earlier animal experiments but challenged by some clinical studies. Wave intensity analysis therefore not only contributes to a better mechanistic understanding of waveform generation in the epicardial arteries, but has great potential of developing into a powerful tool for assessment of the human coronary microcirculation.

The next two chapters are related to the effect of duration of diastole on coronary perfusion. A larger diastolic time fraction (DTF), the relative time spent in diastole, reduces the impediment of flow related to heart contraction. Animal studies where microspheres were used to measure transmural flow distribution over the heart muscle have shown that perfusion of the innermost (subendocardial) layer critically depends on the duration of diastole.

In Chapter 6, we demonstrated that the administration of the alpha1-receptor antagonist urapidil resulted in a prolongation of DTF regardless of heart rate. We
inferred from our data that \( \alpha_1 \)-receptor blockade in our patient group augmented subendocardial perfusion, thereby providing an adjunct mechanism for the well-documented beneficial effect of urapidil after percutaneous coronary intervention.

The model study presented in Chapter 7 is based on a three-layer model of the myocardial wall and was developed using data from the above mentioned previously published animal studies. The maximal conductance of each layer was set to depend on DTF and on perfusion pressure as varied by stenosis severity. The results clearly demonstrated that especially at reduced perfusion pressures, the subendocardium was the first layer to experience a shortage of perfusion at low DTF values (high heart rate), while it was the last layer to become ischemic at high values of DTF (low heart rate). Furthermore, fractional flow reserve, a parameter frequently used for decision-making in the catheterization laboratory, was also shown to depend on heart rate. Both findings have important clinical implications, as endocardial perfusion assessed in clinical stress tests with pharmacologically induced hyperemia likely overestimates endocardial perfusion during real exercise conditions with elevated heart rates.

Chapter 8 discusses the work presented in this thesis. It is concluded that the pulsatile waveforms of intracoronary pressure and flow velocity contain valuable information regarding mechanisms of coronary-cardiac interaction and about coronary microvascular function in humans that cannot be derived from traditional beat-averaged analysis of these signals. Microvascular dysfunction is an increasingly important research area in the pathogenesis of myocardial ischemia. It is therefore to be expected that the exploration of pulsatile phenomena by wave intensity analysis, as well as dynamic indices of stenosis resistance or signal energy will ultimately support diagnosis and treatment assessment in clinical practice.