Cardiac-coronary interactions in humans: Mechanistic Insights from wave intensity analysis
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Link to publication

Citation for published version (APA):
Rolandi, M. C. (2014). Cardiac-coronary interactions in humans: Mechanistic insights from wave intensity analysis

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Summary
Intracoronary pressure and flow-velocity signals reflect the interaction between cardiac mechanics and coronary hemodynamics. In this thesis we explored the origin of the time-varying characteristics of these signals in relation to cardiac mechanics in particular in disease, as result of treatment and interventions.

Chapter 1 provides a general introduction of coronary hemodynamics. General physiological concepts based on averages over the cardiac cycle are treated, followed by an explanation of the flow velocity waveform within the cardiac cycle. This chapter concludes with a description of intracoronary signals as waves propagating in the coronary vessels and their assessment in the time domain. Wave intensity analysis (WIA) is described as a powerful tool to study the pulsatility of these signals, reflecting the interaction between coronary flow and cardiac mechanics.

The clinical studies presented in this thesis are based on intracoronary pressure and flow velocity measurements obtained in patients with coronary or aortic valve diseases. Coronary hemodynamic signals were obtained simultaneously with a dual-sensor guidewire (Combowire) equipped with both a pressure and a flow velocity sensor. Based on these signals, wave intensity analysis was performed.

Full application of wave intensity analysis requires the knowledge of wave speed. The single-point technique (SPc) is usually used to estimate coronary wave speed despite its validation was limited to the systemic circulation only. Chapter 2 presents a direct measure of the wave speed in human undiseased coronary arteries assessing the impact of adenosine and nitrate administration. Together with the intracoronary hemodynamic signals obtained with the Combowire, a micro-catheter equipped with two high-fidelity pressure sensors was inserted in the undiseased coronary artery and allowed the acquisition of two extra pressure signals. The pressure sensors on the micro-catheter are at a known distance of 5 cm allowing the measurement of the wave speed (DNc) based on the time delay between the two signals. Measurements were acquired at resting condition and after vasodilation induced by adenosine and nitroglycerine. We demonstrated that human coronary wave speed is not affected by distal vasodilation. Moreover, we proved that SPc reliably estimates coronary wave speed under resting conditions but not during adenosine or nitroglycerin induced vasodilation. Therefore SPc estimated at rest can serve as surrogate for separating wave intensity signals obtained during hyperemia.

These findings were applied in Chapters 4 and 6 where wave speed was used for wave separation during both resting and hyperemic conditions.

Chapter 3 focuses on the effect of altered coronary-cardiac interaction during the Valsalva maneuver (VM). The patients performed this maneuver with a forcible expiration against a closed glottis. In addition to the intracoronary signals recorded with the Combowire, aortic pressure and left ventricular pressure were measured as well. The Valsalva maneuver was used to induce a sudden increase
in intrathoracic pressure that generates a cascade of events in cardiac mechanics and coronary perfusion. On one hand, following the vena cava compression, cardiac mechanics is strongly depressed at maximum strain of this maneuver. The diminution of cardiac mechanics is reflected by the strong decrease in LV pulse pressure and LVdP/dt. On the other hand, coronary hemodynamics does not reflect the decrease in cardiac mechanics as expected with intact autoregulation since microvascular resistance drops impeding the decrease of flow velocity. However, the energies of all four waves of WIA are depressed reflecting the decrease in cardiac mechanics. Microvascular vasoconstriction must have been compensated by a decrease in the contraction-mediated impediment on coronary blood flow, as confirmed by the reduced coronary wave energies.

We described in Chapter 1 how an unbalance between the oxygen need and oxygen delivery could cause ischemia and subsequently angina. These symptoms can also be present with an aortic valve stenosis (AS) despite unobstructed coronary arteries. With AS, ischemia would be related to the increased compression of the intramural microcirculation because of elevated systolic left ventricular pressure of the subendocardium. This hypothesis was tested in chapter 4 by analyzing the flow velocity profile and wave intensity at rest and during maximum hyperemia in patients with aortic stenosis before and after transcatheter aortic valve implantation (TAVI). In addition, these patients were compared to a control group without aortic stenosis. We demonstrated that AS and TAVI did not produce a major effect on the means per beat intracoronary signal although the pulsatility of these signals was strongly impaired in AS. Especially the systolic flow velocity in AS was reduced compared to normal patients and restored to normal values after TAVI. The forward compression wave (FCW) accelerating systolic flow was not different in magnitude between control and AS but it was delayed with AS. This delay was related to the delay in the peak of aortic pressure and was reduced after TAVI, concomitant with an increase in the magnitude of the wave. The early diastolic backward expansion wave (BEW) was higher in patients with AS than in controls. Likely, in presence of AS the elevated LV end diastolic pressure (LVEDP) increased the intramyocardial vascular volume and hence also the energy of the BEW. The ratio of hyperemic to resting BEW was related to coronary flow reserve (CFR) giving a possible explanation of impaired CFR with undiseased coronary arteries. TAVI caused a similar increase in both resting and hyperemic BEW with minimum change of their ratio consistent with the minimum change in CFR. The TAVI-induced increase in FCW was related to the increase in systolic flow velocity integral indicating a compromised systolic flow velocity with AS that is restored after TAVI. That suggests an acute relief of subendocardial compression in systole. Despite the improvement of systolic flow with TAVI, there is no immediate improvement in CFR and BEW ratio. This indicates a compromised hemodynamic response probably because of the hypertrophy generated by AS. More time is needed to restore pulsatile flow velocity to normal conditions.

Chapter 5 reports the adaptations within the coronary and systemic circulation to exercise in order to explain the warm-up phenomenon in patients with coronary
artery disease. During cardiac catheterization, the patients recruited in this study performed two consecutive exertions bicycling on a supine cycle ergometer. Intracoronary signals were measured with the Combowire downstream of the coronary stenosis whilst aortic pressure was measured with an extra pressure wire. Despite reaching the same workload, patients had less ischemia during the second exertion. We showed that the augmentation and the tension time indices, reflecting the contributions to aortic pressure due to reflections, were lower during the repeat exercise, suggesting a reduction in the afterload at the second exertion. On the other hand, a reduction in coronary microvascular resistance resulted in flow velocity increase on the second exertion. The increase in net BEW reflected a better relaxation of the ventricle during exercise that was more pronounced during the second exercise. We therefore concluded that the warm-up angina phenomenon in patients with effort angina could be explained by a combination of changes in the systemic and coronary circulations that combine to improve cardiac-coronary interaction and enhance myocardial perfusion.

In chapter 6, we present a more detailed analysis in terms of wave intensity of the effect of exercise on cardiac-coronary interaction in patients with coronary artery disease. In order to get more insights about the systemic circulation contribution to exercise, we compared it to right atrial pacing that has minimal effect on the systemic circulation. The pacing condition was analyzed with and without autoregulation intact. Both interventions produced the same increase in heart rate but the pulse pressure increased during exercise while it decreased during pacing. Mean coronary hemodynamic parameters were similarly affected by both interventions, characterized by an increase in coronary pressure and flow velocity and a decrease in microvascular resistance. Contrary to right atrial pacing, exercise strongly affected the systemic circulation, which was reflected in the coronary wave intensity pattern while the beat averaged parameters were similarly affected. While exercise produced strong increase in the forward waves, these were not affected by pacing. The change in the forward waves energies was related to the change in aortic pulse pressure suggesting a strong dependence of these waves on the aortic pressure waveform. BEW and BCW increased with exercise whilst pacing only affected the BCW to a similar extent as in exercise. The rise in LV pressure is faster with both pacing and exercise and it is likely responsible for the wave generation rather than contractility. Exercise also produced the appearance of an extra forward wave that was absent at rest and during pacing. This wave is likely coming from reflections in the periphery that are increased during exercise.

In chapter 7, the results of this thesis are discussed in relation to the mechanisms responsible for the waves. The magnitude of each wave is the consequence of the force by which it is generated and the parameters that cause its attenuation. All waves are generated by the cardiac contraction and relaxation so they are strongly related to parameters of cardiac mechanics such as LVDP/dt. The forward waves are strongly related to aortic pressure waveform. That holds not only for the two dominant waves, forward compression and forward expansion waves, which have the same origin as in aortic wave intensity, but also for the extra wave observed in the coronary wave intensity pattern. We describe in this chapter how
this extra wave comes from the reflection in the periphery and therefore it can be occasionally observed in the coronary artery when wave speed in the aorta is decreased (during the Valsalva maneuver) or when the amount of reflections is increased (during exercise). The energy of the coronary backward waves is modulated by the intramyocardial volume. As for ventricular function, the pressure generated by contraction is likely higher at a higher level of ventricular filling; this is also the case in the intramural vessels. The causal role of intramural blood volume is still hypothetical since, unfortunately, intramyocardial volume could not be measured in our studies. However the results are consistent with the hypothesis that the backward waves have more energy when intramyocardial blood volume is higher.

In the discussion chapter we also noted some methodological limitations of the analyses that were performed in this thesis. Pre-processing of pulsatile signals is an important technical issue. With respect to filtering we had to find the best balance between noise removal and retaining physiological information. This chapter concludes with some recommendations for future research.