Cardiac-coronary interactions in humans: Mechanistic insights from wave intensity analysis
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Chapter 7

General discussion
Until recently, analysis of coronary hemodynamic signals for clinical diagnostic applications was mainly focused on mean flow and pressure values obtained by averaging over the cardiac cycle. Per definition this kind of analysis ignores the time-dependent nature of these pulsatile signals. Coronary pressure and flow velocity waveforms are the result of an intricate interaction of cardiac mechanics, microcirculation, coronary and systemic circulation. Looking beyond means by examining the pulsatility of these signals may help unravel the complicated interaction between these different domains. Therefore, studies on pulsatile signals offer new possibilities for improving our understanding of the influence of cardiac or vascular pathologies on myocardial perfusion. Recent advances in technology allow simultaneous high fidelity measurements of pressure and flow velocity in coronary arteries permitting the application of wave intensity analysis (WIA) to these signals. The introduction of this method made it possible to mechanistically quantify the different contributions to coronary pressure and flow velocity waveforms originating from the aorta and the microcirculation respectively. In this thesis, we applied WIA to understand interaction between cardiac contraction and coronary hemodynamic signals under normal and pathophysiological conditions as well as before and after interventions or treatments.

DETERMINANTS OF PULSATILITY AND WAVE INTENSITY OF THE CORONARY SIGNALS

Variations of pressure and flow in a coronary artery can be combined with WIA into waves of energy corresponding to different moments within the cardiac cycle. Net wave intensity $dI$ is defined as the product of simultaneous local changes in pressure and flow velocity between two successive sample points. By definition, the sign of this product will be positive when pressure and flow are changing in the same direction and it will be negative otherwise. In the coronary circulation, four major distinctive waves are discernible in the $dI$ profile. These waves bear mechanistic information on the typical coronary flow velocity profile with its systolic flow impediment and diastolic dominant perfusion. Additionally, their specific timing within the cardiac cycle allows relating these waves to other hemodynamics or cardiac mechanical parameters. In this way, WIA has the potential to yield new physiological insights for coronary flow dynamics and cardiac-coronary interaction.

The magnitude of a wave is a consequence of the force by which it is generated and the factors that cause its attenuation. To separate these mechanisms is not an easy task since they are often interrelated. An additional problem in humans is the difficulty to vary only one parameter at a time without affecting the others. For example, an increase in contractile forces will not only affect the forces generating the waves but also elicit autoregulatory responses by increased oxygen demand that enhance systolic-diastolic flow differences and thereby wave intensity.
Figure 1: Representation of mechanisms responsible for wave intensity. Cardiac mechanic events are responsible for wave generation in the aorta and in the coronary arteries. The forward waves in the coronary arteries are to a large extent determined by the aortic pressure waveform. The status of the microcirculation accounts for attenuation of the backward waves. MVO2: myocardial oxygen consumption; LVEDP: left ventricular end diastolic pressure; FCW: Forward compression wave; FEW: Forward expansion wave; BCW: Backward compression wave; BEW: Backward expansion wave.

Figure 2: BEW energies under different conditions. The increase in the BEW energy goes in parallel with an expected increase of intramyocardial volume. *p<0.05 compared to the same vessel at resting condition; †p<0.05 compared to normal vessel at the same condition.
The complex interaction of mechanisms responsible for the wave intensity pattern is illustrated in Fig. 1. The mechanical events associated with heart contraction represent the basic source for the generation of all waves. An important factor is contractility that can be influenced positively by a variety of interventions. In case of atrial pacing, contractility is increased by the Bowditch effect or frequency-dependent inotropy, while with exercise, inotropy is additionally augmented by sympathetic activation and increased circulating catecholamines [1]. Counterintuitively, the BCW was similarly affected by both interventions, while contractility levels must have been higher with exercise. The higher contractility with exercise is clear from a 20% higher increase in peak Pa that was measured and increased cardiac output which is the physiological response to exercise. The explanation for similar effects of HR and exercise indicates that not contractility is the final step in affecting the BCW but the rate of change of left ventricular pressure, LVdP/dt during the time of BCW generation. The change in LVdP/dt was not directly measured but can be deduced from the reduction in systolic time which must have resulted in an increased LVdP/dt. It is recognized that the max value of LVdP/dt, LVdP/dtmax, is often used as measure of contractility, but this holds under constant conditions of preload and afterload [2]. Hence, proof of this hypothesis must come from direct LV pressure measurements at different inotropic states of the heart. However, the hypothesis that LVdP/dt is involved mechanistically is also supported by observations on early systolic flow decrease and transmission of PLV to myocardial lymph pressure in early systole [3-4]. It is also consistent with the relation between BCW and LVdP/dtmax found in Chapter 3 with the Valsalva maneuver where probably the inotropic state was not altered either, other than by preload and afterload alterations.

Heart contraction pushes a compressive wave into the aorta. This wave travels downstream towards the periphery but also into the coronary arteries. From reflection points along the aorta, a backward wave is generated which results in a secondary increase of aortic pressure usually expressed by the augmentation index. The second dominant forward wave is the expansion wave resulting from the deceleration of blood at the end of systole. The time difference between the forward waves in the aorta is mainly dependent on the duration of systole, but the time between forward and the backward compression waves depends on the wave speed in the aorta: the higher the wave speed the shorter the time difference. The wave intensity pattern in the coronary arteries is more multifactorial than in the aorta, since coincident waves are also generated in the coronary microcirculation, which is periodically compressed. These backward waves are actively generated by contraction and relaxation of the myocardium: the backward compression wave (BCW) and backward expansion wave (BEW), respectively. The BCW appears at the beginning of systole when the heart starts its contraction before the aortic valve opens and decelerates flow. In contrast, the BEW appears at the beginning of diastole when the heart relaxes and induces a rapid increase in early diastolic coronary flow velocity. The dominant forward compression and expansion waves in the coronary arteries coincide with those in the aorta since they have the same source. A second forward compression wave may be noted in the coronary artery in mid-systole which has its origin in the backward wave traveling upstream in the aorta, which not only will
Figure 3: Model of the coronary circulation. The intramyocardial compliance is represented by a ‘balloon’ that is subjected to compressive forces. This compliance is connected to the large veins by an outflow resistance ($R_{out}$). The inflow resistance ($R_{in}$) can vary depending on the metabolic regulation. Stenosis resistance ($R_s$) is in series with $R_{in}$. Intramyocardial volume ($V_{im}$) is related to the intramyocardial pressure ($P_{im}$). $P_{im}$ equals the product of the inflow ($Q_{in}$) times $R_{out}$ and is added to $P_{out}$.

$P_{im} = Q_{in} \times R_{out}$

Figure 4: BCW energies under different conditions. The increase in the BCW energy follows the assumed increase of intramyocardial volume. An exception is AS at rest where an increase is expected while no difference in the energy was found. *$p<0.05$ compared to the same vessel at resting condition; †$p<0.05$ compared to normal vessel at the same condition.
enter the left ventricle but also the coronary arteries, a phenomenon occasionally observed in this study as discussed below.

Although the force of contraction is at the source of all waves and hence is important in determining the magnitude of the waves, there are modulating factors. For the backward waves in the coronary arteries, intramural blood volume plays an important role. In ventricular function, the pressure generated by contraction at constant contractility is higher at a higher level of ventricular filling; this is also the case in coronary function where a higher degree of filling of the intramural vessels results in higher systolic-diastolic flow differences and hence higher intensity waves. Also, microvascular resistance may be relevant since it co-determines the difference between systolic and diastolic arterial flow and hence the rate by which coronary flow varies. It therefore also affects the magnitude of the waves.

**Backward waves: intramyocardial volume and cardiac-coronary interaction**

In this thesis we have determined wave intensity under different physiological and pathophysiological conditions. Although intramural vascular volume was not directly measured in these studies, it is conceptually an important parameter. For this discussion we have collated in Fig. 2 the intensity of the backward expansion wave under conditions in which a constant contractility is expected. The BEWs have been arranged with increasing magnitude to see whether this order is consistent with increasing intramural vascular volume deduced from physiological reasoning.

The underlying conceptual model is depicted in Fig. 3. Its major component is the compliant microcirculation with outflow resistance draining against coronary venous pressure. The inflow resistance (R_in) is adjustable and represents regulatory properties associated with local autoregulation and metabolic adaptations. The stenosis resistance (R_s) is in series with the microvascular compartment. Pressure in the compliant compartment (P_{im}) results from the product of coronary flow (Q_{in}) and the outflow resistance (R_{out}) added to the coronary venous pressure (P_{out}). Volume in the compliant microvascular compartment (V_{im}) increases with distending pressure (P_{im}). For the sake of argument, we will ignore in this discussion the non-linearities induced by the decrease of resistance and stiffening of the compliant microcirculation with increasing distending pressure [5].

Based on the model in Fig. 3, one may expect that pharmacological vasodilation will result in increased flow and a larger intramural volume, and therefore, an enhanced intensity of the BEW. Such an increase was indeed found for all conditions: normal, coronary stenosis and aortic stenosis, although in the presence of a coronary stenosis it did not reach significance (p=0.09). This is most likely because the vasodilatory capacity is already compromised at rest, hence limiting the volume increase following adenosine-induced vasodilation and thereby, the BEW increase.

At rest, the BEW did not differ between normal and stenosed a vessel, which is explained by a similar baseline flow due to compensatory arteriolar vasodilation distal to the stenosis. In the presence of an aortic stenosis, the BEW at rest was
Figure 5: Collection of FCW (left) and FEW (right) energies at baseline flow (b) and hyperemia (h) as a function of aortic pulse pressure (PPa) at control and following interventions. Different groups of patients at baseline condition have a similar energy at a similar pulse pressure. FW energy and PPa change in concert with different interventions. A decrease in microvascular resistance with adenosine causes an increase in the FW energy for a given pulse pressure. *p<0.05 compared to the same autoregulatory condition at control. †p<0.05 compared to the same vessel at resting condition.

Figure 6: Schematic drawing of the aorta (top) and an epicardial coronary artery (bottom) with a forward wave propagating. In the aorta, the wavelength is shorter than the vessel length, and pressure and flow variations constituting the wave are related via the characteristic impedance of the aorta. In the coronary artery, the wavelength exceeds the length of the vessel and pressure and flow variations constituting the wave are not only determined by the input impedance of the coronary artery but also by the impedance of the microcirculation distributed over many side branches (Z distal vascular bed).
higher than in the normal hearts. This is consistent with an increased intramural vascular volume that follows from the elevated LVEDP that relates to coronary sinus pressure [6]. Vasodilation is expected to further increase microvascular volume. However, the hyperemic flow velocity in AS was less than in normal hearts, hence limiting the expected blood volume increase in this condition, which therefore was likely not bigger than in normal vessels despite the higher LVEDP. We conclude that at the same contractile level, the ordering of the BEW in terms of its energy is consistent with the expected increasing levels of intramural blood volume for the different conditions.

As demonstrated in Fig. 4 the same reasoning generally also holds for the BCW, with the exception of aortic stenosis at rest, where the BCW is not bigger than in the normal condition despite the higher expected volume as discussed above. Most likely, other mechanisms take place that go beyond the information acquired in this thesis. Further investigations are needed to reveal the difference in mechanisms involved in the two backward waves.

**Forward waves: Systemic circulation and cardiac-coronary interaction**

Forward waves in the coronary system are related to arterial systolic inflow and therefore to the systolic component of myocardial perfusion (Chapter 4). Although coronary arterial inflow occurs predominantly in the diastolic phase, this does not imply that systolic inflow is not important. Systolic inflow not only contributes to the net perfusion of the heart and is therefore relevant when the heart is on the verge of ischemia, but it especially reflects the balance of coronary arterial pressure and subendocardial microvascular pressure. When systolic coronary arterial pressure is reduced compared to the compressive forces at the subendocardium, such as in AS, a diminished systolic microvascular volume will have to be restored in diastole, which may be incomplete.

The forward waves originate from the ventricle and travel via the aorta into the coronary circulation. Hence, coronary and systemic forward waves are expected to have the same timing and be affected by the same parameters. While we have not studied systemic and coronary waves simultaneously, our results are consistent with this hypothesis. This is certainly a research topic that deserves pursuing in future work.

As with wave intensity in the aorta, the coronary FWs are related to LVdP/dt (Chapter 3) and a strong relation with aortic pulse pressure was observed (Chapter 6). In Fig. 5, the collective data on the energies of the FCW and FEW are plotted in relation to aortic pulse pressure. Two major observations can be made from these plots. The first one is the relation with aortic pulse pressure; the second is the effect of distal vasodilation as reflected by a higher value during the hyperemic condition. How the aortic pressure waveform and distal vasodilation affect the forward waves is discussed in more detail below.

**Relation with aortic pressure waveform**

Different groups of patients with similar pulse pressure also had similar FW
energy despite the presence of a coronary or aortic stenosis. A causal relationship between the FCW and the aortic pressure waveform is additionally supported by the relation between arrival time in the coronary artery and delay in peak aortic pressure caused by AS (Chapter 4). TAVI partially restored the timing of the aortic pressure peak and therefore also the timing of the FCW. Restoration of systolic waves and coronary wave pattern are certainly indicative for the effect of TAVI on normalization of subendocardial perfusion.

An extra forward compression wave was occasionally observed in mid-systole following the Valsalva maneuver or exercise (Chapters 3 and 6). This wave is not directly related to cardiac mechanics but likely comes from reflection in the systemic periphery. There are several reasons for a concealment of this extra forward compression wave in the coronary system in the majority of cases. 1) The magnitude of the reflected wave was not large enough to be detected in the coronary artery 2) the wave arrived too early to be discernible from the dominant forward wave coming from the ventricle and 3) the wave transmission into the coronary system interfered with the transmission into the left ventricle. Since the impedances do not match, the reflected wave is variably distributed over the different compartments connected to the respective ostia.

The amount of reflections and aortic wave speed in the aorta can be altered by changing the impedance at the reflection site and the compliance of the aorta, respectively. During the Valsalva maneuver, wave speed in the aorta decreases as a result of the increased compliance secondary to the reduction in transmural pressure. In addition, the reflection is also lowered due to the changed impedance [7]. In contrast to the Valsalva maneuver, exercise increases the amount of peripheral reflections but it also increases the wave speed in the aorta by decreasing the compliance [8]. Therefore, both exercise and the Valsalva maneuver, even if for opposite reasons, tend to promote the appearance of this extra wave in the coronary wave intensity pattern.

**Effect of distal vasodilation on forward waves**

In the absence of a coronary stenosis, the energy of forward waves increases with microvascular vasodilation as shown in Fig. 5. This finding is unexpected since forward traveling waves should be relatively insensitive to variation in the downstream resistance. However this is true only for a uniform system where its length is large compared to the length of the wave. As shown in Fig. 6 in a simplified model, this is the case in the aorta but not in the coronary artery where the wavelength exceeds the length of the vessel and multiple side branches introduce non-uniformity. Therefore, while in the aorta pressure and flow variations constituting the wave are related predominantly via the characteristic impedance of the aorta, in the coronary artery, pressure and flow variations are also affected by the downstream microvascular bed impedance.

The effect of microvascular vasodilation is clearly noticeable in undiseased vessels, even in the case of aortic stenosis. In the presence of a coronary stenosis, this effect is diminished or absent due to compensatory dilation prior to administration of adenosine.
METHODOLOGICAL CONSIDERATIONS

Developments in technology made it possible to simultaneously measure pressure and velocity in human coronary arteries by means of a sensor-equipped guide wire. Despite the high accuracy and temporal resolution of these sensors, especially the flow velocity signal can be noisy. This has minimal impact on the derivation of coronary parameters based on cycle-averaged flow and pressure. However, dynamic analysis, especially when involving derivatives, requires some signal conditioning.

In order to extract dynamic physiological information from often noisy signals we used a combination of low-pass filtering and ensemble averaging over selected beats. Filtering reduces noise but also affects physiological information by lowering the dynamic frequency content of the signals. Ensemble averaging over several beats reduces random noise under the assumption that the beats are comparable on physiological grounds. This assumption is not necessarily always true since there may be beat-to-beat variations such as small differences in heart rate or systolic-diastolic duration. Hence, a balance had to be found between diminishing noise by filtering and ensemble averaging without compromising too much relevant physiological dynamic information.

The derivatives of pressure and flow velocity signals needed to perform WIA were obtained by a 3rd order polynomial 19 point Savitzky-Golay filter. Considering an average HR of 70 bpm and our sampling rate of 200 Hz, the 19 points used to calculate the derivatives correspond to 8% of the entire cardiac cycle. At higher heart rates, this filter size may have depressed the magnitude of wave intensity. It should be noted that we used the same filter settings for all conditions, and it is unlikely that the applied signal processing biased our conclusions.

OUTLOOK

In this thesis we have described our endeavor to characterize the mechanisms that determine the intracoronary pressure and flow velocity waveform. However, we only covered a piece of the entire picture. In this final section, some recommendations are given for future research that could yield more insight into cardiac-coronary interaction as well as suggestions to improve the technical tools in applying wave intensity analysis.

Long-term adaptation after TAVI

We presented in Chapter 4 the effect of an aortic valve stenosis on cardiac-coronary interaction and the immediate consequence of TAVI. It would be very useful to know how TAVI affects cardiac-coronary interaction assessed by WIA at longterm follow-up, during which the heart can recover from hypertrophy. A cycle-averaged hemodynamic analysis at 12 months follow-up confirmed restoration of the coronary flow reserve to control values [9]. It is likely that after such a period, also pulsatile coronary hemodynamics would return to values comparable to those in undiseased patients. However, experimental data confirming the normalization of cardiac-coronary interaction are still missing. A full restoration of waves to the control state and their response to physiological stimuli is not trivial. Restoration
will depend on the efficiency of the valve replacement and cardiac remodeling. Since the contractile function of the heart plays such an important role in the pulsatility of coronary flow and wave intensity, it would be very helpful when hemodynamic signals under several conditions could be measured simultaneously with the time-dependent pressure and volume in the left ventricle.

**Cardiac mechanics dysfunction and cardiac-coronary interaction**

Systemic WIA in subjects with compensated heart failure has shown a marked reduction in the wave energy generated by the left ventricle and increased wave reflection, compounding the load on the left ventricle [10]. Since cardiac support and assist devices are used to help the failing heart, it is important to understand their effect on coronary hemodynamics. Some studies have been performed to assess the effect of an intra-aortic balloon pump [11-12] on cardiac-coronary interaction, but the effect of continuous-flow impeller pumps is still unknown. Such studies may help to optimize the operating variables of these devices with respect to optimal myocardial perfusion, which in turn may well support the recovery of failing hearts.

**Microcirculation dysfunction and cardiac-coronary interaction**

WIA is not only useful to estimate the effect of impaired cardiac mechanics on cardiac-coronary interaction, but also to assess the effect of microvascular dysfunction on coronary flow. Diabetes is associated with small vessel disease and impaired endothelial function that affects both peripheral and coronary vessels. WIA has been used for assessment of arterio-ventricular coupling in type 2 diabetes and identification of subgroups with an increased myocardial energy demand [13], but the effect on cardiac-coronary interaction is not yet unknown. Microcirculatory dysfunction will likely affect the intramyocardial volume that we discussed as being an important determinant of the backward waves. An impairment of especially the BEW could lead to a slower or reduced increase in flow velocity and hamper adequate diastolic perfusion.

**Wave speed with coronary stenosis**

Coronary wave speed is an essential parameter for separating wave components in WIA. Almost eight years ago, the single-point technique (SPc) has been proposed to estimate wave speed in arteries from the simultaneously measured pressure and flow velocity signals [14]. Comparison of SPc with the foot-to-foot method in the aorta served as an experimental validation in unobstructed systemic artery, whereas validation of SPc using coronary pressure and flow velocity signals was not available when this thesis started. Moreover, SPc in coronary arteries was found to bring about counter-intuitive results, such as a decrease in wave speed when intraluminal pressure increased after stenting [15]. Similarly, hyperemia due to microvascular dilatation had an implausible effect on SPc-derived wave speed in the larger coronary artery.

These unexpected results led to the study described in Chapter 2, where we compared wave speed estimated with SPc with the time-delay method at rest and during maximal vasodilation. We found that, contrary to the estimate with SPc,
actual wave speed was unaffected by distal vasodilation. Moreover, SPr at baseline compared well with the wave speed measured from the time-delay method. Hence, SPr is a useful technique to assess coronary wave speed at baseline in unobstructed vessels, which can serve as a valid measure for wave speed during hyperemia. One of the reasons for the failure of SPr to assess coronary wave speed at hyperemia may be the effect of hyperemia on the forward waves. Because of the rather long wavelength compared to the length of the coronary artery, the sum of dU in the denominator of SPr is not only the result of the wave transmission properties of the coronary artery, but also of the impedance of the microcirculation. Microvascular vasodilation increases the values of dU for reasons other than related to wave transmission. The higher the microvascular resistance, the less influence it has on dU and the better SPr approached the real wave speed in the coronary artery.

It is important to note that the measurements reported and discussed in Chapter 2 were obtained in normal coronary arteries. The limitation of SPr to assess wave speed downstream of a coronary stenosis still exists. To even further extend the utility of WIA, it would be of great value to fill this gap and find a way to determine wave speed downstream of a coronary stenosis.

**CONCLUSIONS**

Intracoronary pressure and flow velocity waveforms are the results of a complicated interaction of different factors, some of which have been extensively described in this thesis. Characterizing these signals in terms of wave intensity analysis allows identifying the separate parameters responsible for the waveforms during the cardiac cycle. This technique therefore not only provides an important tool to understand the physiology behind the intracoronary signals but, in case of disease, could also open new possibilities for improvements in clinical diagnosis and treatment, specifically targeting the therapies to restore myocardial perfusion.
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