Analysis of pulsatile coronary pressure and flow velocity: looking beyond means
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Chapter 2

Background
2.1. Anatomy and physiology of the coronary circulation

2.1.1. Anatomy of the coronary circulation

The heart maintains blood flow throughout the body and in order to perform this pumping function it needs to be supplied with blood and nutrients. The coronary circulation receives blood from the aorta and distributes it by a branching network of vessels over the epicardium, the outer surface of the heart. These epicardial vessels give rise to the so-called transmural vessels that penetrate the heart muscle or myocardium. The intramyocardial vessels branch into progressively smaller arteries that form the coronary microcirculation. The smallest of these arteries are denoted as arterioles and supply the capillary network. Epicardial veins run alongside the large epicardial arteries.

**Epicardial coronary vessels**

The coronary ostia, arising from two of the sinuses of Valsava, constitute the origin of the epicardial coronary arteries [10, 36, 64, 66]. The left main coronary artery stems from the left ostium and after a short distance from its origin it bifurcates into two major coronary arteries, the left anterior descending (LAD) and the left circumflex (LCx) arteries (Figure 2.1). The LAD courses down the anterior interventricular groove, whereas the LCx runs through the left atrioventricular sulcus. Together they perfuse mainly the left ventricle (LV) and atrium. Furthermore, the septal branches of the LAD supply the interventricular septum and run intramurally. The right coronary artery (RCA) originates from the right coronary ostium and follows the right atrioventricular sulcus. It perfuses primarily the right ventricle and atrium, but also part of the LV. There is naturally considerable variation in the exact distribution of the large coronary arteries between and within species.

Collateral vessels connect the branches of parent epicardial arteries from different regions of the heart and may act as an alternative source of blood supply to parts of the myocardium when the normal route is impeded, for example due to the presence of an epicardial stenosis. Under normal conditions collateral vessels in the human coronary circulation exist in a dormant fashion and start to mature and function only in the presence of an appropriate stimulus, such as ischemia or the presence of a pressure gradient between their perfusion territories.

The epicardial veins can be divided into three systems. The largest portion of the coronary veins drains the LV and converges into the coronary sinus, which in turn empties into the right atrium. The anterior cardiac veins drain the right ventricle and empty into the right atrium as well, but not via the coronary sinus. A smaller system consists of small veins, the Thebesian veins, that empty directly into all four cardiac chambers and may drain as much as 10% of total coronary flow in some conditions. There are many anastomoses between the epicardial veins to direct venous flow to an alternative route in case a vein collapses, for example due to low intraluminal pressure.
Coronary microcirculation

The small arteries (diameter<400 μm) and arterioles (diameter<200 μm) are the primary site of coronary vascular resistance and therefore play a dominant role in the regulation of coronary blood flow [5, 64 66]. These vessels are thus referred to as resistance arteries.

The capillary bed does not have a branching pattern, but resembles more an interconnected network of small vessels with diameters of the same order of magnitude as the diameter of the red blood cells. The capillary wall acts as a semipermeable membrane and has specific transport mechanisms. At this level the exchange of oxygen, electrolytes and nutrients for CO₂ and metabolites takes place.

Blood from the capillary bed is drained into the venules and then via the transmural veins is directed to the epicardial veins.
2.1.2. Cross-talk between the cardiac muscle and the coronary vasculature

Most of the coronary vasculature is embedded in the cardiac muscle and as a result there is mechanical interaction between the contracting myocardium and these vessels [82]. Generation of cardiac contractile force and of intramyocardial pressure, increase in myocardial thickness and stiffness and shortening of the cardiomyocytes are ways via which the contracting heart muscle can affect the intramural vessels and thus coronary flow. On the other hand, a change in vascular diameter or in vessel wall properties, as a response to alterations in intraluminal pressure or smooth muscle cell (SMC) tone, changes perfusion conditions and thereby affects the cardiomyocytes as well.

2.1.3. Control of coronary blood flow

Autoregulation

Autoregulation characterizes the ability of an organ to maintain its blood flow matched to its metabolic needs independently of variations in perfusion pressure. The phenomenon of autoregulation is demonstrated by the so-called autoregulation curves, shown in Figure 2.2 [64, 65]. When coronary perfusion pressure is decreased, but is still within the physiological working range, progressive vasodilation of the resistance vessels ensures that coronary flow is maintained. The plateau of the autoregulation curve shifts upwards with an increase in metabolic demand and this process is referred to as metabolic flow adaptation. At a given perfusion pressure, the difference in flow as dictated by the pressure-flow lines in the presence of autoregulation and during maximal vasodilation yields coronary flow reserve.

![Autoregulation curves at different levels of myocardial oxygen consumption (MV O2). When MV O2 increases, the curves shift upwards, towards higher flow levels. (Figure from [64]).](image)

The resistance vessels are responsible for autoregulation and they can adjust coronary flow by controlling the tone of the SMCs that line their walls and by thereby modifying their diameters. Intraluminal pressure decreases gradually from larger to smaller resistance vessels, indicating that coronary vascular resistance and the mechanisms for control of coronary blood flow reside in all these vessels. (Figure 2.3) [5].
**Mechanisms for coronary blood flow control**

Myogenic response describes the property of small arteries and arterioles to respond to a change in transmural pressure by changing tone, resulting in a diameter change opposite to the pressure stimulus: a decrease in intraluminal pressure will induce an increase in vascular diameter and vice versa [64, 65].

When the vasodilatory capacity of these vessels is exhausted and tone is absent, for example due to ischemia or vasodilatory medication, they react passively to changes in intraluminal pressure and their diameter changes in the same direction as intraluminal pressure [19, 78].

Flow-dependent dilation refers to the property of the endothelial cells to respond to an increase in blood flow by releasing Nitric Oxide (NO) which relaxes SMC tone, thereby inducing vasodilation [64, 65]. Endothelial cells sense the increase in shear stress induced by the increase in flow and the release of NO aims to normalize shear stress rather than to regulate blood flow. Endothelial-dependent hyperpolarizing factor (EDHF) may act as a backup for the NO-mediated flow-dependent dilation system.

The presence or absence of substances that are involved in cardiomyocyte metabolism can also act as a control signal for the regulation of SMC tone [64, 65]. Changes in metabolic activity or oxygen supply can be communicated to the resistance vessels with signals such as adenosine concentration and myocardial tissue oxygen pressure.

Finally, neurohumoral factors can also affect SMC tone.
2.1.4. Differences between subepicardial and subendocardial perfusion

Perfusion to the subendocardium is more impeded by myocardial contraction than subepicardial flow [64-66]. When the coronary blood flow control mechanisms are intact, flow distribution over the subepicardium and subendocardium is relatively uniform [2]. This is achieved by the appropriate adjustment of vascular resistance at a local level and, provided that the vasodilatory capacity of the resistance vessels in the subendocardium is sufficient, demand and supply can still be matched in this myocardial layer.

![Graph A](image)

**Figure 2.4:** (A): Subendocardial conductance is positively related to DTF under conditions of maximal vasodilation. It further depends on perfusion pressure (Pc) and for the same DTF subendocardial conductance decreases when coronary perfusion pressure drops. (B): On the contrary, DTF and coronary pressure have no significant effect on subepicardial perfusion. (Redrawn from [13]).

However, when active coronary vasomotion is eliminated, subendocardial conductance becomes inversely dependent on heart rate and decreases with decreasing diastolic time fraction (DTF), whereas subepicardial perfusion is not affected (Figure 2.4) [2, 12, 13]. DTF is the relative duration of diastole with respect to the duration of the heart cycle. The dependence of maximal subendocardial
conductance on DTF is indicative of the strong mechanical effect of myocardial contraction on subendocardial perfusion and perfusion of this layer of the heart muscle will be critically impaired by an increase in myocardial compressive forces and/or a decrease in DTF.

Further, when the vasodilatory capacity is exhausted, subendocardial perfusion will critically depend on the driving perfusion pressure, as indicated in Figure 2.4, whereas subepicardial perfusion remains unaffected.

2.2. Pulsatility in coronary pressure and flow

2.2.1. Phasic coronary pressure and flow

Figure 2.5 depicts the main features of coronary pressure and flow velocity in the angiographically normal LCx of a 59 year old patient, just before a stent was placed to treat a 66% DS in the RCA. The similarity between the aortic and the coronary pressure waveforms is evident, but the contour of coronary flow velocity is distinctly different. At the onset of LV contraction, systolic flow velocity abruptly decreases and starts to rise only after the opening of the aortic valve and the beginning of LV ejection. A second dip in flow velocity coincides with the closure of the aortic valve and thereafter diastolic flow increases again until approximately mid-diastole. Subsequently, coronary flow falls with diastolic perfusion pressure. Systolic flow is lower than diastolic flow and this inhibition of coronary arterial flow in systole is called Coronary Systolic Flow Impediment (CSFI). The observation that coronary flow is lower when perfusion pressure is higher indicates that CSFI is associated with cardiac contraction.

![Figure 2.5](image)

Figure 2.5: Recordings from the angiographically normal LCx of a 59-year-old patient, just before removal of a 66% DS in the RCA. Top panel, coronary flow velocity. Bottom panel, aortic (Pa, shaded grey) and coronary pressure (Pd, continuous black line).

2.2.2. Models explaining coronary systolic flow impediment

Until 50 years ago the effect of heart contraction on coronary flow was unclear, with researchers debating whether heart contraction had an inhibiting [54] or augmenting [84] effect on flow through the intramyocardial vascular bed. The different results were partly due to the different types of vessels where the observations were made: in the arteries blood flow decreased during contraction, but in the veins flow was maximal during systole and almost absent in diastole. At present there is abundant proof that coronary perfusion is impeded by cardiac contraction [62, 82].
Cardiac contraction causes intramural blood volume to vary throughout the cardiac cycle, a phenomenon that has been denoted as intramyocardial pump action [63]. In systole blood volume is squeezed out of the intramyocardial vessels, but intramural blood volume is restored during diastole. The level of perfusion impediment depends on the balance between these two processes. At higher HR there will be less net intramural vascular volume and thereby on average coronary resistance will be increased.

However, there is no unanimous agreement about the mechanism by which contraction results into intramural vascular volume reduction. At first it was assumed that the so-called tissue pressure formed the ‘motor’ of the intramyocardial pump. Tissue pressure had also been used earlier to explain flow impediment according to the Waterfall model, a model assuming that the intramural vessels would collapse instantaneously when extravascular pressure would exceed intravascular pressure [62, 82]. Later, an alternative model was presented, describing the intramyocardial pump action in analogy to LV function, where the time-varying elastance was considered to be responsible for pressure generation and transmural vascular volume displacement.

In the following sections an overview of the different models that have been developed for explaining CSFI will be given. Such an overview is not only of historical interest. The different models, as developed over time, focused on a mechanism in isolation. However, none of these mechanisms is able on its own to fully explain CSFI. Rather, they all play a part in the complicated interaction between the heart muscle and the vasculature that leads to CSFI. Therefore this overview mainly serves to describe all the possible mechanisms for CSFI, one of the most important aspects of coronary pathophysiology.

**Systolic Extravascular Resistance Model**

This model was particularly promoted by Gregg and coworkers in the 1950’s [16, 62, 66]. It assumed that coronary resistance in systole was higher than in diastole due to extravascular compression, without further specifying the mechanism. However, it was assumed that this compression effect faded away quickly in diastole and that therefore at the end of diastole coronary resistance could be measured unrelated to the compression effect. We now know that diastole is normally not long enough to allow the intramural vessels to get completely inflated [64]. Nevertheless, from direct observations of intramural and subendocardial arterioles, it is established that their resistance is higher in systole than in diastole [85].

**Vascular Waterfall Model**

This model [8, 66, 82] assumed that the radial stress in the ventricular wall generated a tissue pressure which varied over the myocardial wall, from LV pressure at the endocardium to thoracic pressure at the epicardium. It further assumed that this tissue pressure would act on the outer surface of the intramural vessels as a fluid pressure (Figure 2.6). In case tissue pressure exceeded coronary arterial pressure, coronary flow would completely cease. With a lower tissue pressure, only intramural veins were expected to locally collapse and at this collapse point intramural pressure would be equal to tissue pressure. Hence, according to this model, flow would be equal to the difference between arterial and tissue pressure divided by the vascular resistance between the coronary main artery and the point of collapse.
Background

The waterfall model provided a good framework for explaining why subendocardial perfusion is more impeded than subepicardial perfusion. However, it ignored the resistance variations during the heart beat and could not account for retrograde systolic flow. Retrograde flow commonly occurs in the septal artery at low perfusion pressures and may also be observed in the left main coronary artery at low pressure during vasodilation [63]. Importantly as well, the waterfall model would predict a phasic venous outflow pattern similar to the arterial one, while essentially these two signals are 180 degrees out of phase.

**Intramyocardial Pump Model**

A major conceptual addition of the intramyocardial pump model to the other models was the compliance of intramural vessels [62, 63, 66]. The intramural vascular compartment was represented by a lumped compliance. The resistance of the intramural vessels was distributed into an inflow and an outflow resistance that roughly corresponded to the resistance of the arterioles and the venules, respectively (Figure 2.7). It was postulated that cardiac contraction squeezes blood volume out of the compliance, reducing arterial inflow and augmenting venous outflow. The elasticity of the intramural vessels would then form a restoration force for intramural volume, augmenting arterial inflow in the subsequent diastole and decreasing venous outflow. This model was later expanded to incorporate resistance variations during the heart beat as a result of the varying diameters of the intramural vessels.
Figure 2.7: The Intramyocardial Pump model. The compliance of the intramural vessels is represented by a ‘balloon’ that is subjected to compressive forces. The rate of change of intramural volume, $dV/dt$, represents the capacitive flow and is equal to the difference between inflow, $Q_{in}$, and outflow, $Q_{out}$. (From [65]).

**Varying Elastance Model**

The varying elastance model [31, 33, 80, 82] is an intramyocardial pump model as well, but it hypothesized that the pump action was generated by the time-varying elastance of the myocardial wall rather than by tissue pressure, as assumed in the original presentation of the intramyocardial pump model [63]. The elastance model was first proposed by Suga et al. [71] to describe the pump function of the LV (Figure 2.8). According to their model, the increase in elastance during systole would increase pressure in the LV cavity, resulting in ventricular ejection. Similarly, the varying elastance model assumed that this increase in the elastance of the myocardial wall would also increase intramyocardial pressure around the intramural vessels, resulting in squeezing blood out of these vessels.

Evidence for this concept came from the simple observation that in isolated hearts coronary flow was pulsatile even when no ventricular pressure was generated [31, 32, 34]. It was therefore suggested that the myocardial elastance has a direct effect on the vessels submerged in the tissue. Moreover, by independently manipulating cardiac contractility and LV pressure in the isolated and maximally vasodilated cat heart at a controlled fashion, it was found that contractility has an order of magnitude stronger effect on the amplitude of coronary arterial flow than LV pressure [33]. Later it was demonstrated that in an empty beating dog heart subendocardial perfusion was hardly different from the situation where normal ventricular pressure was generated, clearly supporting this hypothesis [76].

However, based on the elastance model one would expect the same perfusion impediment in the subepicardium as in the subendocardium, whereas that is not the case as discussed above [13]. Moreover, it has been demonstrated that ventricular pressure is transmitted to the coronary arterial system in systole [30] and that especially in early systole LV pressure is transmitted to the interstitial space, as illustrated from epicardial lymph pressure measurements [18].
Figure 2.8: The elastance model for the LV proposed by Suga et al. [71] and its analogy to the elastance model for the intramyocardial vessels. The end-diastolic and end-systolic pressure-volume lines are determined by the properties of the cardiac muscle. At the end of diastole the LV is filled up to its end-diastolic volume, when contraction starts. Pressure in the LV rises isovolumically until it exceeds aortic pressure and the aortic valve opens. During the ejection phase blood volume is squeezed out of the LV under rather constant pressure. After the closure of the aortic valve the isovolumic relaxation phase starts with both the aortic and the mitral valves closed. When LV pressure has dropped below left atrial pressure the mitral valve opens and the LV starts to refill. The presence of the isovolumic lines in the LV pressure-volume loop is due to the valves. The pressure-volume loops for the intramural vessels will also be delineated by the same end-systolic and end-diastolic lines, but because of the absence of valves the change in volume will be continuous throughout the heart cycle. (From [62]).

2.3. Stenosis hemodynamics

A stenosis is a local narrowing of the flow duct, caused by deposition of atheromatous plaque in the vascular wall. The residual vessel lumen inside the stenosis can be circular, elliptical or slit-like and the stenosis itself may be positioned symmetrically or eccentrically with respect to the axis of the unobstructed vessel. Further, a stenosis can be rigid or compliant [59]. If the whole circumference of the stenotic vessel segment is not covered by plaque, part of the stenosis will consist of normal flexible vascular wall, which will passively move due to changes in transvascular pressure. Such a stenosis would be a compliant stenosis, because its geometry changes during the heart cycle, as transmural pressure changes. The following sections refer to characteristics of rigid stenoses [64, 65]. Stenoses are a common occurrence in the large epicardial arteries, but not in the microvessels.

2.3.1. Functional effect of a stenosis on coronary flow

Pressure drop

The most severe effect of a stenotic lesion on coronary flow is induced by the translesional pressure drop. This reduces driving perfusion pressure to the vascular bed distal to the stenosis and thereby compromises coronary perfusion. Young et al. [86, 87] measured the total pressure drop (ΔP) across artificially generated stenoses in the
femoral and carotid arteries of large dogs and found that it can be satisfactorily described by the equation:

$$\Delta P = AQ + BQ^2 + C \frac{dQ}{dt} \tag{2.1}$$

where Q is flow through the lesion and A, B and C are constants that depend on the geometry of the stenosis and the rheologic properties of blood. It is emphasized that the factors A and B are critically dependent on the inverse fourth power of the diameter of the stenosis [37]. The first term of the equation corresponds to the law of Poiseuille and describes the pressure drop because of the viscous friction exerted on the bloodstream by the stenotic wall. The second, non-linear term refers to the pressure loss caused by the convergence and divergence of flow as it enters and leaves the stenosis, respectively. According to the law of Bernoulli, velocity is increased and therefore pressure must be decreased as the blood flow enters the stenosis. At the exit, because of the increase in area, flow velocity drops and this is accompanied by a partial pressure recovery, but some energy is permanently lost due to flow separation and eddy formation at the downstream end of the stenosis. The third term gives the pressure drop due to the inertia of blood, because in the presence of pulsatile flow, energy is consumed in order to accelerate the flow in alternating directions. For clinically significant stenoses, only the contribution of the first two terms is important and therefore pressure-drop increases quadratically with flow (Figure 2.9). A direct implication of this equation is that stenosis resistance ($\Delta P/Q$) is flow-dependent.

![Diagram showing pressure drop-flow velocity lines for stenoses of various degrees (indicated as percent reduction in lumen area). The experimental points are fitted with a quadratic equation of the form $AQ+BQ^2$. Steeper curves correspond to more severe degrees of stenoses. (Redrawn from [86]).](image)

**Figure 2.9:** Pressure drop-flow velocity lines for stenoses of various degrees (indicated as percent reduction in lumen area). The experimental points are fitted with a quadratic equation of the form $AQ+BQ^2$. Steeper curves correspond to more severe degrees of stenoses. (Redrawn from [86]).

### Distal vasodilation as compensation of stenosis resistance

A coronary stenosis may develop over time unnoticed, because the coronary resistance vessels can react by vasodilation in order to maintain perfusion matched to oxygen demand. However, this autoregulatory response to compensate for the
presence of a developing stenosis limits the capacity of the resistance vessels to further dilate in response to an increase in oxygen demand related to exercise, resulting in angina pectoris and raising the risk for myocardial ischemia.

This risk of ischemia is higher in the subendocardium than in the subepicardium, because of the more pronounced effect of extravascular compression on that layer of the heart wall. As mentioned above, the subendocardium is critically dependent on the duration of diastole and on perfusion pressure.

There are several compensatory mechanisms by which the heart can withstand a pressure drop induced by a stenosis. A decrease in distal pressure to values below the autoregulatory range may lead to an increase in DTF [39]. The heart can also delay the onset of ischemia by decreasing myocardial oxygen demand in order to better match the diminished supply [11]. A very efficient way of the heart to prevent ischemia is the formation of collateral vessels which supply the myocardial region that is dependent on the stenotic vessel with blood coming from non- or less diseased arteries.

Effect of stenosis on pulsatility in coronary flow

A stenosis acts as a low-pass filter on the flow velocity waveform and makes its profile more flat. In contrast, pulsatility in distal perfusion pressure increases and the shape of the coronary pressure signal resembles more LV rather than aortic pressure.

2.3.2. Structural changes in the resistance vessels induced by a stenosis

The mechanisms of structural adaptation of the coronary microcirculation distal to epicardial stenoses are not yet fully understood [77]. According to clinical evidence, the long-term reduction in microvascular tone, because of the permanently low perfusion pressure distal to coronary stenoses, may induce compensating outward remodeling of the resistance vessels [78]. As a result, after stenosis removal and pressure restoration, the resistance vessels are not able to adapt immediately to the new perfusion conditions with vasoconstriction. Therefore, it is not only the hyperemic coronary resistance that has been decreased due to outward remodelling, but also the ability of the resistance vessels to generate tone [78]. On the other hand, studies on isolated small coronary arteries contradict these conclusions. Cannulated microvessels exposed to transvascular pressure profiles resembling those distal to a coronary stenosis, to the extent that such profiles can be defined, exhibited inward remodelling after a few days, which was reversed to outward remodelling with a calcium channel blocker [61].

2.3.3. Functional evaluation of the coronary circulation in humans

Clinically used hemodynamic indices

Coronary Flow Velocity Reserve (CFVR) is defined as the ratio between maximal flow velocity (obtained during exercise or with vasodilatory drugs) and coronary flow velocity at rest [25, 67]. This ratio can be measured by a Doppler-sensor-equipped guidewire. A cutoff value of <2 is indicative of a stenotic lesion that can lead to ischemia and therefore needs to be treated. CFVR is a combined measure of the capacity of both the epicardial arteries and the distal microvascular bed to achieve maximal velocity. This index was developed as a surrogate for Coronary Flow Reserve
(CFR), which is based on flow rather than flow velocity measurements. The disadvantage of this index is that its calculation depends on the accurate determination of baseline flow velocity and on the achievement of maximal vasodilation.

Fractional Flow Reserve (FFR) describes the maximum achievable myocardial blood flow in the presence of a stenosis, given as a percentage of the flow that could be theoretically accomplished if the artery was normal [25, 67]. In clinical practice this index is calculated as the ratio of distal over aortic pressure during maximal hyperemia, under the assumption that venous pressure is negligible relative to aortic and coronary pressure and that minimal microvascular resistance is not different distal to a stenotic as opposed to a reference vessel. A cutoff value of <0.75 is associated with inducible ischemia. This index is based on pressure measurements alone and does not depend on the determination of baseline conditions, but is still dependent on maximal vasodilation.

When both pressure and flow velocity measurements are available, it is possible to calculate a velocity-based index of stenosis severity under hyperemic conditions (HSR) as the ratio of pressure drop across the stenosis divided by flow velocity through it [25, 40, 67]. This index refers to the impediment to maximal flow induced by the stenosis itself. A cutoff value of >0.8 mm Hg/cm/s is indicative of inducible ischemia.

**Pressure drop-flow curves**

Pressure drop-flow curves can be easily measured during and after pharmacologically-induced vasodilation by applying a dual-sensor guidewire (combowire) which combines a pressure and a flow velocity sensor [25]. When pressure drop (ΔP) and velocity are averaged per beat, these curves follow the theoretical quadratic course and provide a comprehensive way of visualizing the hemodynamic performance of the stenosis within the physiological working range. The steeper the curve, the more severe the stenosis (Figure 2.9) [14, 86]. Additionally, the ΔP-velocity curves allow the detection of collapsible stenoses, since these stenoses induce an hysteresis-like behaviour, where the ΔP-velocity relation at increasing velocity is different from that of decreasing velocity (Figure 2.10) [60]. A further advantage of this approach is that the improvement of stenosis hemodynamics induced by percutaneous coronary intervention (PCI) can be readily demonstrated. After each step of PCI the ΔP-velocity curves drop in a clockwise fashion, approaching the shape of the reference vessel curve and maximum achievable velocity increases.
Figure 2.10: Pressure drop-flow velocity relationships recorded distal to a collapsible stenosis. Before treatment (pre) the presence of a loop is indicative of a collapsible stenosis. The curves become progressively less steep after balloon angioplasty (balloon), stent placement (stent) and upsizing the stent (UPstent), approaching the shape of the curve recorded in an angiographically normal vessel (ref). (From [60]).

**Nuclear medicine imaging techniques**

In nuclear medicine clinical information is derived from the measurement of the distribution of a radiopharmaceutical administered to the patient. The imaging is mostly carried out with gamma-cameras and the derived information is about function rather than anatomy.

Single-Photon Emission-Computed Tomography (SPECT) and Positron Emission Tomography (PET) are the techniques that are commonly used for myocardial perfusion imaging. In terms of imaging quality PET generally provides higher spatial resolution and has enough accuracy to allow for the measurement of myocardial blood flow in absolute terms [23, 52]. On the other hand the cost for dedicated PET cameras remains significant.

PET imaging performed under rest and stress provides qualitative and quantitative information about perfusion at different areas of the myocardium under different hemodynamic conditions and enables the non-invasive assessment of CFR. In that way the non-invasive evaluation of the functional significance of a coronary stenosis and the identification of the myocardial regions that are more prone to ischemia is possible.

Because abnormalities in the control of the coronary microcirculation are often involved in ischemic heart disease [55-57], techniques for the assessment of myocardial perfusion are of great clinical importance.
2.4. Wave propagation in the coronary circulation

2.4.1. Wave speed

Historical note

Thomas Young in his Croonian Lecture [88] was the first to tackle the subject of the propagation of the pressure pulse in elastic arteries. Two hundred years ago, based only on fundamental principles of physics and using experimental work by Stephen Hales [17] to support his arguments, he estimated the velocity of the ‘transmission of the pulsations of the heart’ in man to be approximately 15.5 ft/s or 4.7 m/s. This value is in good agreement with current wave speed measurements in the upper thoracic aorta of the man [35, 41] and the dog [29, 38, 41].

Importance of wave speed as a physiological parameter

In arterial blood flow mechanics the terms wave speed and pulse wave velocity (c) are interchangeably used to describe the velocity of propagation of the pressure pulse generated by the heart. This velocity is superimposed on the convective velocity of blood (U), causing forward waves to travel with speed (c + U) and backward waves with speed (c - U) [21].

Wave speed is not only an important physiological parameter per se, but it is also a basic parameter needed in Wave Intensity Analysis (WIA). According to the one-dimensional wave propagation theory, wave speed is inversely dependent on vessel wall distensibility (D):

\[ c = \frac{1}{\sqrt{\rho D}} \]

where \( \rho \) is blood density [4, 27]. The physiological importance of wave speed stems from this relation on vessel wall properties, which allows it to be used as an index of local vessel wall stiffness and thus as a potential identifier of risk of cardiovascular disease. Knowledge of wave speed also allows for the separation of pressure and velocity into forward and backward components, by implementing WIA. This separation is helpful for studying the mechanisms of blood flow dynamics in the arteries.

Techniques for measuring wave speed

Wave speed can be measured using two pressure sensors with a known distance between them and by determining the time of travel of the foot of the pressure wave from one sensor to the other [38, 41, 45]. This two-point technique is known as the foot-to-foot method. Features on the pressure contour other than the foot may be used, such as the peak of its first time-derivative [15] or points along the rising limb of the pressure wave at a predefined percentage of peak systolic pressure [44]. The precision and reproducibility of the two-point methods mostly depend on the accuracy with which the foot or any other identification point can be defined on the pressure pulse. Due to the nature of the method, the resulting wave speed is the average wave speed along the arterial segment that is contained between the two measuring locations. This two-point technique has not only been applied in various animal and human vascular segments [41], but also in the LV of the dog [79], yielding values ranging from 1 m/s during diastole to 10 m/s during systole.

Although two-point methods are commonly used for wave speed calculations, single-point techniques that yield local wave speed are also popular, but rather laborious in
their application. Based on Fourier analysis, the impedance spectrum of the interrogated vascular bed can be calculated from pressure and flow measurements and then characteristic impedance may be derived by averaging the impedance moduli over a range of higher frequencies where the effect of wave reflections on the impedance spectrum is minimal [46, 83]. A different method for calculating characteristic impedance directly in the time domain has been presented by Dujardin et al. [9]. When characteristic impedance is known, pulse wave velocity can be derived from it [4]. Applying the method of Dujardin et al. a value of 2-3 m/s was calculated in the pulmonary artery of the dog [22].

![PU-loop recorded in a latex tube with a diameter of 1 inch. A single, semi-sinusoidal wave was introduced into the system and measured pressure was plotted against measured velocity for the duration of the semi-sinusoid and until the system returned to steady state conditions. The slope of the initial part of the PU-loop (dashed line) is equal to \( \ell \). (From [28]).](image)

A new method based on simultaneous pressure (P) and velocity (U) measurements at a single location has been recently proposed [27]. The method originated from the observation that according to the water-hammer equation, in the presence of waves traveling only in one direction, P and U are linearly related and the slope of the P-U plot, with U as the independent variable, is proportional to wave speed. Provided that
a period of unidirectional wave travel occurs during the cardiac cycle, the slope of the linear portion of the PU-loop can be used for the determination of wave speed (Figure 2.11). The reproducibility and precision of the PU-loop method are dependent on the ability to identify the linear part. This method performed well when tested against the foot-to-foot method [28] and has been applied both on invasive and noninvasive measurements of P and U in various vascular beds [29, 89]. Using the PU-loop method, values of approximately 7 m/s have been reported in the radial and brachial arteries and of the order of 5.5 m/s in the carotid artery of healthy subjects [89]. A similar method based on flow-vessel cross sectional area loops has also been recently proposed [51].

A different single-point technique uses simultaneous measurements of velocity and vascular diameter at a single location and was tested in human carotid artery measurements obtained non-invasively with diagnostic ultrasound and echo-tracking respectively. These measurements were used to derive the stiffness parameter of the artery and from that wave speed [20]. The technique performed well when compared against the PU-loop method and yielded values of approximately 7 m/s in normal subjects.

Based on Wave Intensity Analysis, a single-point technique that also requires simultaneous pressure and velocity measurements was presented last year [7]. The advantage of this method over the PU-loop method is that it uses measurements during complete heart cycles without any limitation about unidirectional waves. In the human aorta wave speed determined by this method was compared to the value derived by the foot-to-foot method and satisfactory agreement was found between the two, with values of the order of 8 m/s. In the context of the same study the method was also applied in human coronary arteries, but this application will be discussed in detail in the next section.

**Wave speed in the coronary arteries**

Despite the wide range of techniques available for wave speed measurements, up to date there is a very limited number of studies on coronary wave speed. The coronary bed presents special challenges for the methods reviewed above. The coronary arteries are rather short, small in diameter and tortuous. As a result, locating a straight vessel segment with relatively uniform properties, large enough diameter to accommodate two pressure sensors without much disturbance in the flow pattern and sufficiently long to allow for enough distance between the two sensors is a difficult task. Therefore two-point techniques are not easily applicable in the coronary arteries. Single-point methods based on Fourier analysis require the properties of the arterial system under study not to be time-varying, a condition not satisfied by the coronary circulation because of heart contraction [75]. Further, due to the nature of wave generation in the coronary arteries, forward and backward traveling waves are simultaneously present along these vessels, rendering the application of single-point methods such as the PU-loop not possible.

In 1979 two independent animal studies on coronary wave speed were published [1, 53]. The experimental work reported by Arts et al. [1] was conducted in open-chest dogs. The heart was exposed and pressure was measured at two positions along the left anterior descending artery, approximately 2-3 cm apart from each other. An ECG-triggered pressure pulse-generator was connected to the abdominal aorta and a pulse was generated, timed to arrive at the coronary bed 100ms after the closure of
the aortic valve. The time difference in the arrival of the pulse at the proximal and distal site was measured and coronary wave speed was found to be 8.6 m/s at a perfusion pressure of 100 mm Hg [1].

The study of Rumberger et al. was conducted on open-chest horses [53]. Coronary pressure was simultaneously recorded at two positions approximately 2 cm apart from each other and the sensors were successively moved along the left anterior descending artery, roughly covering the range from 2 to 15 cm distal to the left coronary ostium. The arterial wall was gently tapped in order to create a 5-10 mm Hg pressure pulse superimposed on the propagating pressure wave and the time difference in the arrival of the artificially induced waves at the two pressure sensors was measured. Measured wave speeds ranged from 4 to 11 m/s, depending on the level of coronary pressure and the distance from the ostium [53].

The highly invasive nature of these techniques renders them unsuitable for application in humans. Davies et al. recently proposed a new single-point technique that they tested in the aorta and they subsequently applied in the coronary arteries [7]. They obtained simultaneous intracoronary pressure and flow velocity measurements from patients with normal coronary angiograms in the left main stem, left anterior descending artery and left circumflex artery. Wave speed was calculated using a formula derived from Wave Intensity Analysis on the basis of minimization of net Wave Intensity. Coronary wave speed was 20.4 m/s on average, not significantly different in different coronary arteries. Coronary wave speed increased with age and decreased after administration of isosorbide dinitrate in the left main stem by 43%, reaching a value of 9.3 m/s [7].

2.4.2. Assessment of traveling waves: Impedance Analysis

Theory

Impedance Analysis (IA) is the method conventionally used for the assessment of propagating waves in the arterial system. According to the Fourier theorem every periodic signal can be written as a series of harmonics of appropriate amplitude and phase. Measured pressure and flow in the arterial system can be therefore subjected to Fourier analysis. Spectra of the modulus and of the phase of input impedance can be derived by dividing the amplitudes of pressure and flow and by subtracting their phase angles, respectively. The basic harmonic for these spectra is the heart rate frequency. Thus, vascular impedance is a concept similar to vascular resistance, but describes resistance to oscillatory flow at various frequencies. The spectrum of vascular impedance provides valuable information regarding the behavior of the arterial tree where it was measured and the interaction between the heart and the specific vascular system. These aspects of vascular IA have been reviewed extensively [41, 45, 46], but no emphasis is placed on how this technique can be used for the separation of the measured pressure and flow waves into their forward and backward components.

From the input impedance modulus it is possible to derive characteristic impedance ($Z_c$), which is input impedance in the absence of wave reflections. It is usually calculated by averaging the impedance moduli over a range of (high) frequencies where fluctuations in the impedance spectrum due to wave reflections can be considered almost completely diminished, but other frequency bands can also be
used [46]. Characteristic impedance is a real number in large vessels and independent of frequency [74, 81], contrary to input impedance which is complex and frequency-dependent. For the general case of $Z_c$ being a complex number, the method for the separation of the measured waves into forward and backward components has been thoroughly described by Westerhof et al. [83]. Briefly, the reflection coefficient $\Gamma$ has first to be calculated for each harmonic and subsequently the Fourier components of the forward and backward pressure and flow waves can be derived per harmonic. The contours of the separated waves can then be reconstructed in the time domain by adding the harmonics.

A tacit assumption for this method of analysis is that pressure and flow in the system under study are linearly related and that the properties of the system do not vary with time. The requirement for stable conditions means that when the arterial system is in a transient state, like for example during the Valsava maneuver, IA must be applied with great caution. The coronary circulation presents special challenges for this method, because both the assumptions of non-linearity and time-invariance are questioned.

Pythoud et al. [50] reformulated the equations for wave separation presented by Westerhof et al. [83] for the purpose of taking into account the effects of dissipation and nonlinearities. They concluded that for in vivo applications the linear method is sufficient, because compared to the non-linear method not only does it not induce errors larger than 10%, but in addition it is considerably more simple to use. An earlier attempt for wave separation in elastic conduits, with a fully non-linear method based on the Split Coefficient Matrix method, led however to the conclusion that [69] application of linear analysis for wave separation in non-linear systems leads to errors.

**Some applications in the circulatory system**

The implementation of Impedance Analysis in human pressure and flow measurements evolved in parallel with the advances in the applicable in humans measuring techniques. The majority of human IA studies found in the literature are on the subject of wave reflections.

Murgo et al. [42] demonstrated that in normal humans a more oscillatory aortic input impedance spectrum is associated with a larger late systolic rise in aortic pressure, which is induced by the later arrival of the reflected waves from the terminal abdominal aorta. The same group applied aortic IA in subjects with no cardiovascular disease while they were performing the Valsava maneuver [43]. Impedance Analysis was performed only during the steady part of the three phases of the maneuver (control, strain and post release) in order to abide by the theoretical restrictions of the method. Manipulating the magnitude and timing of the reflections by means of the changes induced in the arterial system with the Valsava maneuver, altered the magnitude of the backward waves and thereby the shape of the aortic pressure contour. Impedance Analysis performed in the ascending aorta and the pulmonary artery explained in terms of differences in the magnitude of the reflected waves, the differences between aortic and pulmonary pressure and velocity contours [74]. When either systemic resistance was decreased with nitroprusside or pulmonary resistance was increased with serotonin, the reflected waves respectively decreased in the aorta and increased in the pulmonary artery. These pharmacological interventions resulted in the recorded waveforms in the two vascular trees to show more resemblance to each other. A methodology for the analysis of wave reflection and transmission through stenoses, based on IA and wave separation, was proposed by Stergiopulos et
al. [68] and yielded good results compared to in vitro experiments. The way wave reflections in the aorta differ between healthy subjects and patients with Marfan’s syndrome (MFS) was recently tested using wave separation analysis as well as other methods [58]. The study was based on non-invasive measurements of pressure and flow and it demonstrated that the stiffening and dilation of the proximal aorta in MFS patients is not accompanied by profound changes in indices of wave reflection. Finally, reconstruction of the aortic pressure waveform from peripheral pressure and velocity measurements was also achieved with IA, by separating peripheral pressure into its forward and backward components and subsequently shifting these components in time, according to wave speed and vessel length [70].

2.4.3. Assessment of traveling waves: Wave Intensity Analysis

Theory

Wave Intensity Analysis (WIA) is an alternative method for the assessment of traveling waves in the cardiovascular system. It is based on the method of characteristics, a technique widely-used in gas dynamics. The problem of wave propagation in elastic arteries was first addressed with the method of characteristics less than two decades ago by Parker et al. [48] and Parker and Jones [47] and since then the theoretical foundation they developed has been applied in a variety of vascular beds. WIA is a time-domain method and assumes that every wave can be reconstructed by the superposition of infinitesimal wavefronts. No assumption regarding the periodicity of the interrogated signals or the linearity of the system under study is necessary.

The derivation of Wave Intensity (WI) based on the method of characteristics is formulated in Chapter 9 of this thesis (Appendix). WI is the product $dP \cdot dU$, where $dP$ and $dU$ are the incremental changes in measured pressure and flow velocity between successive time intervals. WI has dimensions of power per unit area and refers to the power carried by the waves traveling in the blood stream and not to the waves propagating in the vessel wall. Waves traveling in the same direction as flow (forward waves) make a positive contribution to the product and waves traveling in the opposite direction (backward waves) a negative contribution. As a result, in the presence of simultaneously running forward and backward waves in an artery, WI is positive for dominant/net forward waves and negative for dominant/net backward waves. This is the property of WI WIA takes advantage of, because it makes the distinction between forward and backward waves simple [47].

The way Wave Intensity Analysis is applied to simultaneous pressure and velocity measurements is presented in Chapter 5 of this thesis and has also been extensively presented elsewhere [6, 22, 26, 27, 72].
An example of a typical WI contour in the ascending aorta is shown in Figure 2.12. Each peak (‘a’, ‘b’ and ‘c’) corresponds to an individual wave. Positive peaks denote forward waves and negative peaks denote backward waves. Peak ‘a’ is associated with increasing aortic pressure and is therefore a forward compression wave. Peak ‘b’ is associated with decreasing aortic pressure and is a forward expansion wave and peak ‘c’ is a backward compression wave. Compression waves push blood flow towards the direction they travel, whereas expansion waves suck blood flow away from their traveling direction. In case a forward and a backward wave occur simultaneously, what is seen on the net WI profile is the superposition of the two. However, when wave speed is known, it is possible to separate WI into forward and backward components (Figure 2.13) and study the waves without influence from each other. The area of the peak of each wave corresponds to the energy carried by that wave, normalized to the cross-sectional area of the vessel.
Figure 2.13: Separated wave intensity from pressure and flow velocity measurements at the ascending aorta of a dog, recorded while the upper thoracic aorta was totally occluded. Net wave intensity is indicated by the thick solid line. The thin solid line represents separated wave intensity (forward wave intensity is always positive and backward is always negative). The dashed lines show separated wave intensity when a wave speed of ±20% of the value derived from the PU-loop method was used. (From [27]).

Comparison: Impedance Analysis-Wave Intensity Analysis

Wave Intensity Analysis has several advantages compared to Impedance Analysis [3, 47, 49]. The major difference between the two methods is that the Impedance method is applied in the frequency domain whereas WIA is a time-domain tool. This makes WIA results easier to interpret, because relating events during the cardiac cycle to waves arriving at specific times is straightforward, whereas this information is lost in the frequency spectrum. Further, WIA makes no assumptions about periodicity of pressure and flow or about the arterial system being linear and not varying in time, whereas these assumptions are incorporated in the Impedance method. As a result, the Impedance method is not suitable for application in cases of irregular heart rhythms or in cases of vascular beds with varying resistance over time, like the coronary system. Finally, another fundamental difference between the two methods is that unlike IA, which expresses pressure and flow waves as a numerical Fourier series, WIA assumes that any macroscopic wave can be considered as a succession of incremental expansive or compressive wavefronts.

Applications in the coronary arteries

A brief review of WIA applications in various vascular beds is given in Chapter 9 of this thesis (Appendix). This section will refer only to coronary applications.

The first application of Wave Intensity Analysis in the coronary arteries was presented in 2000 [72]. The study was conducted in open-chest dogs and pressure and flow velocity were simultaneously measured in the LCx. The recorded pattern of WI (Figure 2.14) demonstrates a compression wave propagating from the microcirculation during isovolumic contraction, generated by the compression of the intramural vessels. This is followed, after the opening of the aortic valve, by a compression wave traveling
towards the opposite direction and associated with the rising aortic pressure. During LV relaxation an expansion wave traveling towards the microcirculation develops due to decreasing aortic pressure and is dominant until the closure of the aortic valve, when it is replaced by a dominant compression wave traveling in the same direction.

![Figure 2.14: A: LCx coronary flow velocity (U LCx) and pressure (P LCx), aortic pressure (P Ao) and left ventricular pressure (PLV) during one heartbeat. B: Net coronary wave intensity, derived from U LCx and P LCx. C refers to compression waves and E to expansion waves. For further explanation please refer to text. (From [72]).](image)

This wave is induced by the brief augmentation in pressure when the aortic valve closes. As LV relaxation continues, an expansion wave from the microcirculation becomes the dominant wave in the LCx and is generated by the release of the compression imposed on the intramural vessels [72]. This study demonstrated how WIA can be used to separate the influence of aortic and microcirculatory events in coronary pressure and flow. A later study conducted from the same group in the same experimental setting focused on the compression wave from the microcirculation and its determinants [73]. Cardiac contractility was modulated with paired pacing and coronary resistance with infusions of vasodilators and vasoconstrictors in the LCx. It was found that the energy carried by this wave increases with cardiac contractility and coronary conductance. It was further demonstrated that the energy of this wave is proportional to coronary systolic flow impediment, CSFI. This finding and the timing of the wave suggest a potential mechanistic explanation for CSFI [73].

The first application of WIA in human coronary arteries was presented in 2006 [6]. In subjects with normal coronary angiograms, simultaneous pressure and velocity
measurements were obtained in vessels of the left heart. The wave pattern was not qualitatively different from what had already been presented by Sun et al. [72], but it was also shown that it is not different between different left coronary arteries. It was further pointed out that the expansion wave originating in the microcirculation during diastole is the largest wave during the cardiac cycle and it is mainly responsible for the increase in diastolic coronary flow. It was however shown that in patients with LV hypertrophy this wave decreases with increasing LV wall-thickness, suggesting potential changes in the flow pattern and impaired coronary perfusion in this group of patients.

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