REVIEW

Coronary structure and perfusion in health and disease

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Blood flow is distributed through the heart muscle via a system of vessels forming the coronary circulation. The perfusion of the myocardium can be hampered by atherosclerosis creating localized obstructions in the epicardial vessels or by microvascular disease. In early stages of the disease, these impediments to blood flow are offset by dilation of the resistance vessels, which normally compensates for a decrease in perfusion pressure or increased metabolism. However, this dilatory reserve can become exhausted, which in general occurs first at the deeper layers of the heart wall where intramural vessels are subjected to compressive forces related to heart contraction. In the catheterization laboratory, guide wires of 0.33 mm diameter are available that are equipped with a pressure and flow velocity sensor at the tip, which can be positioned distal to the stenosis. These signals provide information about the impediment of the stenosis on coronary flow and allow for the evaluation of the status of the microcirculation. However, the interpretation of these signals is strongly model-dependent and therefore it is of paramount importance to develop realistic models reflecting the anatomy and unique physiology of the coronary circulation.

Keywords: coronary circulation; microcirculation; autoregulation; stenosis; waves; physiological indices

1. Introduction

The heart is the same as other organs in that it needs a supply of blood in order to function. The vascular bed responsible for this blood supply is the coronary circulation. When blood supply to the heart is impeded by disease either in the large vessels or the small vessels forming the microcirculation, ischaemia (lack of oxygen supply) may result and subsequently myocardial cells may die (infarction). It is obviously important to prevent infarction since it limits cardiac function, induces arrhythmias and may result in death. Coronary artery disease (CAD) is a major

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cause of mortality worldwide despite the fact that currently available strategies to lower individual risk factors and treat evident coronary artery stenoses have reduced the cardiovascular event rate by 20–30%. Therefore, developing improved modalities for the diagnosis and the treatment of coronary disease is important for both an increased quality of life and a reduction of the cost associated with CAD across the EU which, for example, amounted to almost 1% of to 1999 gross domestic product and to almost 11% of total national health expenditure in the UK.

Options for the treatment of CAD range from medication to transcutaneous interventions with catheter-based techniques and bypass surgery. While these options provide successful therapeutic strategies for CAD, it is important to improve our insights into all factors involved in myocardial perfusion, to which biomedical engineering can contribute by providing a comprehensive model of the function of the coronary circulation. Such a model should provide a rational basis for the interpretation of perfusion data obtained in control and exercise conditions. The aim of this paper is to describe the basic principles of anatomic design of the intramural coronary circulation as well as its function in order to facilitate the understanding and interpretation of data on perfusion distribution and epicardial arterial signals.

This paper is intended for all those with an interest in the interdisciplinary nature of a fascinating field in which basic insights acquired over many decades of studies on the anatomy, biophysics and physiology of the coronary circulation are beginning to affect clinical applications. The paper is in no way meant to cover all aspects in that process and it certainly does not review all clinical literature on the topic. For the clinicians it may provide some insights into the concepts underlying the indices on which they make clinical decisions and for the basic scientists it sketches the clinical practice and the developments one may anticipate in model-based support for diagnosis and therapy.

2. Coronary anatomy

The coronary circulation has two feeding arteries, a left main artery and a right coronary artery (RCA), that originate from the aortic valve area at the root of the aorta. The aortic valve is a tricuspid valve and each valve leaflet is mounted on the rim of a semi-spherical structure, the sinus of Valsalva, in such a way that enables them to close before the reversal of flow through the valve area (Spaan *et al.* 1975; van Steenhoven & van Dongen 1986). The two coronary arteries each originate from a sinus of Valsalva and traverse and branch over the surface of the heart, the epicardium. Branches from these epicardial vessels penetrate the free walls of the left and right heart chambers as well as the septum that they have in common. The RCA perfuses the free wall of the right ventricle and part of the left ventricle, while the left main artery splits approximately within 1 cm into the left anterior descending (LAD) and left circumflex arteries that perfuse the left ventricular (LV) free wall and the septum. This distinction is important because the right ventricle generates much less pressure than the left ventricle and therefore the interaction between muscle contraction and intramural blood vessels is different (Hoffman & Spaan 1990; Westerhof *et al.* 2006). The greater compression of intramural vessels in the left ventricle results in a systolic coronary flow that is lower in systole than in diastole, as is discussed below.
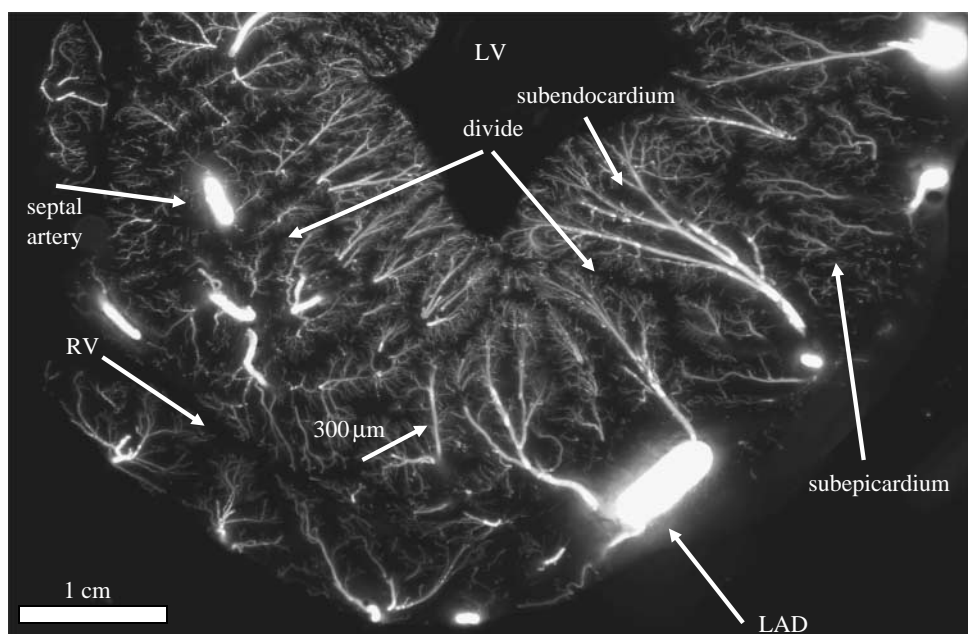
Figure 1. Organization of intramural vessels. The picture is from a fluorescently labelled cast measured in the imaging cryomicrotome and represents a maximal intensity projection of a tissue slab of approximately 2 mm. Smallest vessels visible have a diameter of 40 μm. LV, left ventricular cavity; RV, right ventricular cavity. The vessel labelled 300 μm indicates the level of microvascular organization distal of which all control actions of individual vascular segments are interacting.

Figure 1 illustrates the organization of the intramural blood vessels in a tissue slab of approximately 2 mm at the midsection of the heart, as obtained by an imaging cryomicrotome (Spaan *et al.* 2005; Bennink *et al.* 2007; Rolf *et al.* 2008). With this technique, coronary arterial vessels down to a diameter of 10 μm are filled with a fluorescently labelled plastic that is then allowed to harden. Subsequently, the heart is frozen and placed in the cryomicrotome where it is sliced into 40 μm sections at a time. Fluorescent images are obtained from the bulk after each slice is cut. In figure 1, several structures and locations are identified. The LV cavity is clearly visible. The tissue layer adjacent to the LV cavity is called the subendocardium and when we refer to this layer in this paper we assume that it includes approximately one-third of the ventricular wall. Similarly, one-third of the outer layer of the ventricular wall is referred to as subepicardium and the remaining middle portion as mid-myocardium.

In the lower left of the picture, a piece of the right ventricular (RV) free wall is visible. When preparing the tissue, no attention was paid to keeping the RV cavity inflated and hence the RV free wall rests on the septum, the wall that separates the two ventricular cavities. The large vessel at the bottom is the LAD artery, which branches off from the left main coronary artery and runs along the groove where the free wall of the right ventricle is attached to the left ventricle. There are no major arteries within the free wall of the left ventricle. Smaller transmural vessels penetrate the heart muscle perpendicularly from the larger epicardial vessels and divide intramurally into smaller branches down to the

smallest arteries and arterioles that form the domain of the microcirculation. There are larger arteries running within the septum, which branch off in all directions in a similar way as the transmural vessels in the LV free wall.

Images obtained by this technique clearly suggest divides between perfusion territories as indicated in figure 1. The question of how well perfusion areas in the heart are compartmentalized is relevant for understanding how ischaemia, i.e. the underperfusion of muscle tissue, is distributed in the myocardium, and how this may turn into infarction, i.e. permanent damage and scarring of muscle tissue, affecting cardiac function. In this regard, it is rather important to understand the relationship between the organization of these compartments and the anatomy of the heart muscle. It is well known that infarction in one part of the heart is less disruptive to cardiac function than in other parts and that it is not just a matter of affected tissue mass. For example, papillary muscle at the endocardium is connected with tendon to the leaflets of the inlet valves of the ventricles and assists them in withstanding the ventricular pressure in systole. Ischaemia or infarction of these muscles will reduce the efficiency of the heart as a pump.

The cardiac muscle cells, myocytes, are anatomically well organized in fibres and layers (LeGrice et al. 1995), and the structure of this force-generating network must bear a relationship to the vascular structure as revealed by the cryomicrotome. However, detailed studies relating the microvascular bed to myocyte organization have not yet been performed and are currently not possible with the imaging cryomicrotome.

Since this imaging technique has a limited resolution, one cannot tell whether very small vessels run across the divides between adjacent compartments. Some studies demonstrate that the capillary bed is continuous and inter-connected over large distances, with different terminal arterioles feeding the same network. Hence, a capillary may receive blood from more than one arteriole (Bassingthwaighte et al. 1974) and capillary networks could thus bridge these divides. However, other studies detected sharp separations between tissue regions perfused by different major coronary arteries, in which casting material filling the capillaries could not leave the respective perfusion territories of different supply arteries. Microscope observations of the border zones revealed a system of capillary end loops (Okun et al. 1979).

Where there are anatomical connections between perfusion territories, an area at risk might still receive blood supply in a distributed way across anatomical divides by capillary pathways. Moreover, such cross-linking pathways may form the substrate for the growth of new and larger vessels known as collateral vessels. It is well known that large areas of the myocardial tissue may be rescued by and depend on collateral function.

Some 30 years ago, the concept of a salvageable border zone between healthy and infarcted tissue was discussed, because in histological slices myocardium islands of normal tissue were found within infarcted tissue. However, serial slices uncovered that these islands formed part of continuous peninsulas of tissue (Factor et al. 1978). It is most likely that these peninsulas are related to microvascular structures as shown in figure 1, thereby underlining the concept of strict divides between perfusion territories.

There is great need for more detailed analyses of the structure of coronary anatomy as can be obtained by the cryomicrotome or by other high-resolution methods such as micro-computed tomography (Lee et al. 2007). Such analysis

enables the prediction of flow distribution over the vascular network based on real anatomy. This must be considered as an important step forward, beyond model attempts that are based either on statistical characteristics of branching of the coronary arterial tree obtained by casting methods (VanBavel & Spaan 1992; Kassab *et al.* 1993; Kassab & Fung 1994; Dankelman *et al.* 2007) or on hypothetical rules for vascular network development (Schreiner *et al.* 1995). Although these emerging anatomical models successfully describe fractal flow heterogeneity over tissue segments between 0.1 and 1 g, they fail to predict the difference between subendocardial and subepicardial perfusions (Beard & Bassingthwaighte 2000). It is important to note that much of the computational infrastructure for integrated modelling of the coronary circulation has been realized, including the effect of cardiac contraction on coronary flow distribution, but it is still awaiting more realistic anatomical data (Smith *et al.* 2000; Smith 2004).

3. Coronary physiology

In a healthy condition, coronary blood flow is well adapted to the metabolic needs of the heart. With severe exercise, myocardial oxygen consumption may increase by up to four times its value at rest (Berne 1964). Since extraction of oxygen is practically maximal in the coronary system, blood flow has to increase more or less proportionally to this increased oxygen demand. Judging from measurements at the level of large coronary arteries, the coronary flow control system seems rather perfect. When oxygen consumption is kept constant, coronary blood flow is constant as well and independent of coronary arterial pressure variations. When pressure is kept constant, flow varies linearly with variations in oxygen consumption (Vergroesen *et al.* 1987*b*). However, studies employing labelled microspheres revealed that flow distribution is rather heterogeneous when considering tissue regions smaller than 1 g. A similar conclusion is drawn from measurements of oxygen saturation in venules with cryogenic spectroscopy, where a wide distribution is found, with oxygen saturation varying from below 5% up to 60% (Weiss & Sinha 1978).

That the vascular system is not distributing flow homogeneously, at least not in all conditions, follows from NADH (reduced form of nicotinamide adenine dinucleotide) fluorescence distribution as demonstrated in figure 2. NADH fluorescence indicates areas of oxygen-poor tissue and has been measured from the surface of saline-perfused rat hearts (Ince *et al.* 1993). Under normoxic conditions, NADH levels are low because it is mainly produced under ischaemia. When the heart is made hypoxic, NADH fluorescence is more or less homogeneous over the heart surface as shown in figure 2*b*. When the perfusion medium is then switched to normoxic, some regions turn NADH-free earlier than others as demonstrated in figure 2*c*. Hence, the microvascular bed gives rise to heterogeneous distribution of blood flow and oxygen and therefore some areas are more prone to ischaemia than others.

The coronary vascular volume forms a dynamic entity and is composed of larger and smaller arteries, capillaries and smaller and larger veins. Apart from the influence of anatomical factors on oxygen distribution, one also has to consider the interaction between the perfusion and the function of the heart. All intramural vessels are distensible and deformable, since stiff vessels would make cardiac
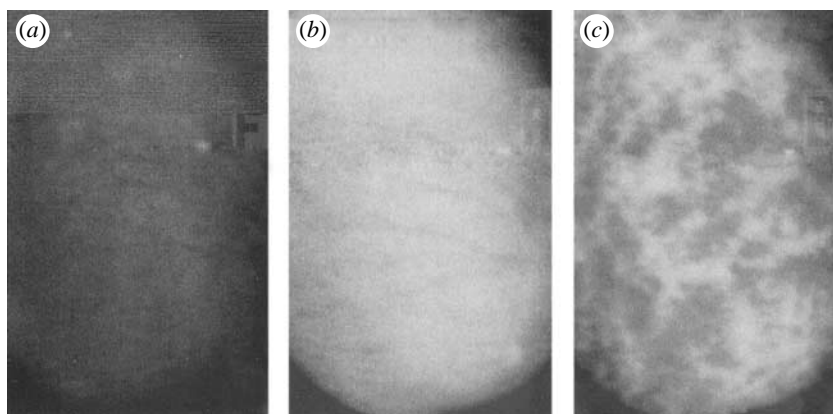
Figure 2. NADH fluorescence from the epicardium of a Langendorff-perfused rat heart under three different perfusion conditions. (*a*) Normoxic conditions and only autofluorescence is visible. (*b*) Perfusion medium was switched to one with a low oxygen concentration (hypoxic). (*c*) Perfusion medium was switched back to one with a normoxic value (transient). The patchy pattern indicates that the time of arrival of oxygen varies highly over the tissue.

function impossible. Several observations demonstrated that the degree of filling of the vascular bed interacts with cardiac function (Gregg & Shipley 1944; Bai *et al*. 1994). Especially in the dilated coronary vascular bed, an increase in perfusion pressure will increase the oxygen consumption of the heart at a constant level of mechanical performance. This is called the Gregg effect or the water hose effect. The resulting increase in oxygen consumption can even be measured in a transient situation when a vasodilator is given and capillary pressure increases owing to the flow increase (Dankelman *et al*. 1996). It is therefore important to keep distending blood pressure in the myocardium as low as possible. This design principle provides a rationale for the high oxygen extraction in the coronary circulation, as mentioned above. A high oxygen extraction corresponds with high arteriolar resistance, thereby reducing flow to a level that is just sufficient for heart function. A lower arteriolar resistance would make the heart mechanically less efficient. This interaction between the perfusion and the heart function requires that a comprehensive model of coronary blood flow control not only in-cludes feedback from metabolism to the tone of smooth muscle in the walls of resistance vessels, but also the effect of perfusion of capillaries on metabolism (Dankelman *et al*. 1999).

The heart controls its blood flow at the organ level. That is important because otherwise heart transplants would not be possible. However, the nervous system has a modulating role (Vergroesen *et al*. 1999). Neural control of blood flow to the heart is often exerted in a feed-forward manner. Hence, when heart activity is increased by neural signals, the coronary system anticipates by vasodilating before the metabolic feedback signal for vasodilatation arrives at the resistance vessels (Mohrman & Feigl 1978; Miyashiro & Feigl 1995; Stepp *et al*. 1996; Feigl 1998).

The crucial messenger responsible for local flow control has long been sought, but no factor has yet been identified. Release of a vasodilator such as adenosine has been suggested to be responsible for metabolic flow adaptation. In this scenario, a disturbance of flow resulting in too little oxygen supply would trigger

the metabolic chain to produce more adenosine, which in turn would cause vasodilation and an increase in blood flow. However, administration of an enzyme that reduced tissue adenosine levels did not disturb the characteristics of coronary blood flow control (Hanley *et al.* 1983). It has been shown that endogenous adenosine remains below vasoactive levels and, hence, adenosine release functions more as an escape mechanism during oxygen shortage when it is produced by myocardial cells in larger quantities (Stepp *et al.* 1996). The fate of adenosine in tissue is complex since it is strongly compartmentalized and different from the interior of myocytes where it is produced, to the intercellular space where its concentration depends on transmembrane and transcapillary transport, and to blood where it is rapidly metabolized. A detailed model of all these processes allows estimation of adenosine concentration at one location from the measurement somewhere else (Kroll *et al.* 1992). This model of Kroll *et al.* can be regarded as a precursor in the development of the current virtual physiological human (VPH) activities. Although adenosine is not likely to be important in normal blood flow control, its interstitial concentration reaches vasoactive levels during ischaemic conditions.

When considering the possible role of a vasodilator in the control of blood flow, one has to realize that a vasoconstrictor is needed in order to provide the resistance vessels with tone, since otherwise vasodilators have no effect (Cornelissen *et al.* 2002). Indeed, vasoconstrictors such as endothelin are present in cardiac tissue and their concentrations are linked to metabolism as well (Merkus *et al.* 2000, 2002). Moreover, blood flow control models based on tissue oxygen tension as the controlled parameter describe rather well the adaptation of blood flow to increased oxygen demand and the maintenance of a stable flow level at constant oxygen consumption when arterial pressure is changed (Drake-Holland *et al.* 1984; Vergroesen *et al.* 1987*b*). However, there is no direct proof that oxygen is the molecule affecting smooth muscle tone and thereby the essential link in metabolic flow control.

It may well be that the search for the single messenger for coronary flow control will never be successful. It is certain that a cascade of biochemical and biophysical processes is involved in the control mechanism (Duncker *et al.* 2008; Trzeciakowski & Chilian 2008). This complexity may be essential to ensure a robust control of coronary blood flow that is less vulnerable to a variety of disturbances. The flow control function is actually distributed over a series of vessels (Chilian *et al.* 1989) rather than a focal point whereby a small portion of tissue would be controlled by a single type of arteriole, contingent upon its proximity to the capillaries or its diameter.

All arterial vessels with diameters smaller than 400 μm are involved in flow control, since pressure gradually decreases in vessels below this size (Chilian *et al.* 1989). There is an arrow in figure 1 pointing to a vessel of 300 μm diameter and the flow and pressure distribution in the tissue region dependent on that vessel is affected by resistance changes of all vessels in that region. One important player in coordinating the response between larger and smaller resistance vessels is flow itself. Owing to short diffusion distances, the smallest arterioles are under the influence of metabolism and will dilate when local metabolism demands more supply. This local dilation will not be sufficient to meet the demand, but it will augment flow in the more upstream vessels. This flow elevation will increase wall shear stress at the endothelium, which triggered

by mechanotransduction will in turn produce the potent vasodilator nitric oxide and stimulate vasodilation of the larger, upstream resistance vessels (Jones *et al.* 1995).

4. Coronary blood flow and cardiac contraction

The coronary vascular system is subjected to the forces of cardiac contraction and its blood volume is lower in systole than in diastole. The average per beat blood volume depends not only on perfusion conditions, such as the degree of vasodilation and perfusion pressure, but also on parameters related to cardiac contraction. Since coronary inflow occurs predominantly during diastole, time-averaged intramural blood volume decreases with increasing heart rate, which shortens diastole. These intramural volume changes are especially apparent when long diastoles are induced (Kajiya *et al.* 1986; Vergroesen *et al.* 1987*a*). These observations are important because, when coronary flow is estimated from wash-in or wash-out curves of contrast, assumptions with respect to intramural blood volume are needed (Bos *et al.* 1995), but in general it is assumed that this volume is constant.

Coronary blood flow is pulsatile (see figure 4) and displays a typical biphasic pattern, even under experimental conditions where coronary pressure can be kept constant. In the left coronary arteries, systolic flow is lower than diastolic flow despite the higher inlet pressure during systole. Systolic flow can even be retrograde when intramural pressure exceeds arterial pressure (Spaan *et al.* 1981*b*). These variations in coronary arterial flow are directly coupled to the contraction-related intramural blood volume variations. The interaction between flow variations and contraction is referred to as the intramyocardial pump (Spaan *et al.* 1981*a*), whose action is most obvious from pulsations of coronary venous flow that is much higher in systole when blood is squeezed out of the intramural vascular bed. These contraction effects in reducing intramural blood volume must relate to an increase of coronary microvascular resistance (MR) induced by compressive forces such as contractility and ventricular pressure.

The mechanisms by which cardiac contraction influences the coronary circulation are not yet fully understood. It is evident that there is an intramyocardial pump action but the generator of the pump is not clear. The group of Westerhof suggested an analogy with the elastance model describing the pump function of the left ventricle (Krams *et al.* 1989; Westerhof 1990). In that model, pressure in the cavities of the heart muscle is generated as the stiffness of the myocardial wall, frequently termed elastance, rises during systole. The generated pressure is larger when the cavities are filled to a higher degree (Krams *et al.* 1990). For the left ventricle this mechanism eventually leads to systolic outflow through the aortic valve, but for the coronary system it causes impediment of arterial inflow and augmentation of venous outflow during systole. However, the increased stiffness of the wall also interferes with the transmission of LV pressure to the heart muscle and the embedded coronary vessels. In the beginning and end of the systole, the wall stiffness is low and LV pressure is readily transmitted to the lumens of the intramural vessels (Han *et al.* 1993; Spaan 1995). By contrast, this pressure transmission is inhibited by the stiffer myocardium in the middle of the systole (Kouwenhoven *et al.* 1992). This process
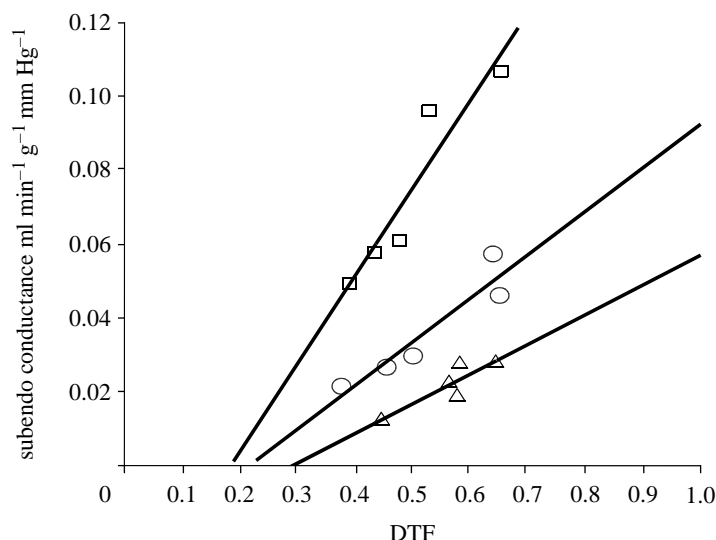
Figure 3. The conductance of the subendocardium (subendo) as a function of the diastolic time fraction (DTF), for three different levels of coronary perfusion pressure, P_c. These data clearly demonstrate the effect of cardiac contraction on myocardial perfusion. The intercepts with the DTF axis indicate that a minimum of DTF is needed to have any endocardial perfusion. P_c: squares, 93 mm Hg; circles, 73 mm Hg; triangles, 40 mm Hg.

is further complicated by the colocalization of intramural arteries and veins within the myocardial tissue. Hence, during cardiac muscle contraction, a decrease in volume of an artery will be accompanied by an increase in volume of the corresponding vein (Vis *et al.* 1997). Obviously, when MR changes are imposed by the flow control of the myocardium, this will affect not only the time-averaged flow but also the flow pulsatility. Cardiac–coronary interactions will be further discussed below in relation to the ensuing wave patterns in the coronary arteries.

As stated above, coronary blood flow can normally increase by a factor of three to four, which implies that the coronary vascular bed is overdesigned to fulfil its function for cardiac performance under non-exercise conditions. At rest, the dilation of the resistance vessels can easily compensate for the increased resistance induced by cardiac contraction. However, in the presence of vascular disease, e.g. a proximal stenosis, the resistance vessels have to dilate to compensate for the pressure loss in the diseased vessel. At rest, this will prevent ischaemia, but not during exercise when demand for flow increases and the increase in flow will further increase the pressure drop over the stenosis. Hence, the myocardial region supplied by the diseased artery can become compromised.

Diastole is needed to refill the intramural blood volume expelled during systole. Hence, the more time spent in diastole, the higher the intravascular volume and the higher the vascular conductance. The relative duration of diastole within a heartbeat is expressed as diastolic time fraction (DTF). DTF is a major determinant of subendocardial perfusion. Figure 3 shows illustrative results from a study in which fluorescent microspheres were injected at different perfusion

conditions in the cannulated left main coronary artery of anaesthetized goats. After the experiment, the hearts were removed and a measure of flow per 100 g of tissue was obtained by determining microsphere density. This was done for three adjacent layers of the ventricular wall. The conductance of each layer was then calculated as the ratio between flow and the arteriovenous pressure difference. For a given perfusion pressure, subendocardial conductance decreased when DTF was reduced by increasing heart rate. At a given driving pressure subendocardial conductance is proportional to flow. This underlines the nonlinear characteristics of myocardial perfusion. Moreover, the flow in the subepicardium is hardly dependent on DTF and hence it is plausible that the subendocardium is more vulnerable to ischaemia (van den Wijngaard *et al.* 2008).

The DTF–subendocardial conductance lines intercept the DTF axis. Hence, for the perfusion pressures studied, subendocardial perfusion is not possible even when some time in diastole is left and certainly not when the heart would be in permanent systole.

The dynamics of the contraction process, resulting in variations in compressive forces, coronary arterial pressure and intramural blood volume, make the system rather difficult to analyse (Kouwenhoven *et al.* 1992). In addition, coronary vessels are stretched and shortened when the heart contracts in systole and ventricles are distended in diastole, respectively. Moreover, all vessels are elastic and their diameters change as a function of the transmural pressure difference across the vascular wall (Spaan *et al.* 2006). Despite these complicated interactions, linear system analysis is often applied and vascular compartments are described by simple resistances and compliances (Canty *et al.* 1985; De Bruyne *et al.* 1994). Since nonlinear systems behave linearly within a limited range of signal variations, these models may be successful in predicting pressure and flow variations, but the estimated parameters from such models rarely bear a direct relationship to biophysical properties. In particular, the change of vascular resistance with intraluminal pressure may conceal the intramyocardial compliance from such measurements (Spaan *et al.* 2000). A more precise analysis of the coronary microvascular circulation is needed to achieve more realistic parameter estimation from functional measurements of coronary flow and pressure.

5. Clinical quantification of coronary vascular disease

Traditionally, the diagnosis of coronary stenosis severity was based only on angiography. A lot of effort has been put into developing image processing methods to predict functional parameters of haemodynamic stenosis severity (Siebes *et al.* 1996). However, the clinical significance of a coronary stenosis cannot be fully characterized based on geometry alone. Over the past 15 years, catheter-based instruments have been developed that enable a more direct assessment of this physiological significance. Initially, guide wires with Doppler crystals at the tip (Doucette *et al.* 1992) became available to measure coronary blood flow velocity. The wire tip is advanced distal to a stenosis and a bolus of adenosine is administered that dilates the resistance vessels, resulting in a transient hyperaemic flow response. The relative increase in average per beat flow velocity, peak hyperaemic velocity divided by velocity at rest, is denoted as

coronary flow velocity reserve (CFVR; Gould & Lipscomb 1974; Hoffman 1984; Wilson *et al.* 1985). The poor predictive accuracy of anatomical stenosis parameters such as per cent diameter stenosis or minimal stenosis diameter was confirmed in a large group of patients by a large variability of this physiological index, CFVR, for stenoses of intermediate severity (Piek *et al.* 2000). About a decade later, guide wires with pressure sensors at the tip were introduced (De Bruyne *et al.* 1994) to assess functional stenosis severity based on the pressure gradient caused by the stenosis. The ratio between the pressure distal to the stenosis, P_d, and aortic pressure, P_a, obtained during maximal hyperaemia, was denoted as fractional flow reserve (FFR). It represents the percentage of normal flow that would be available in the absence of the stenosis. More recently, guide wires have been developed which combine both a Doppler crystal and a pressure sensor at the tip and thereby enable the calculation of velocity-based stenosis resistance (SR) and MR (Meuwissen *et al.* 2002; Siebes *et al.* 2004).

Treating a stenosis with balloon angioplasty or stent placement is not without risk and such an intervention is not always the best choice, especially in relation to recurrence of the disease. Clinical decision making by the interventional cardiologist is supported by these functional indices that are derived from physiological measurements in the catheterization laboratory. In large-scale clinical trials, threshold values indicating a stenosis that causes inducible ischaemia have been determined for these indices in comparison with non-invasive stress tests. The so-called cut-off value associated with a positive treatment decision is less than 2 for CFVR, less than 0.75 for FFR and more than $0.8 \, \mathrm{mm\,Hg\,cm^{-1}\,s^{-1}}$ for SR. One problem is that these fixed threshold values may result in conflicting advice for a given stenosis, depending on whether the decision is based on velocity- or pressure-based indices. A comparison between FFR and CFVR has shown that this was the case for approximately 30% of intermediate lesions (Meuwissen *et al.* 2001).

The reason for the discrepancy between outcomes of FFR and CFVR can be traced back to the models of the coronary circulation that were used to derive these indices (Spaan *et al.* 2006). These models often oversimplify the factors determining coronary perfusion. In particular, the pressure and heart rate dependency of coronary resistance are frequently not considered (De Bruyne *et al.* 1994), while it has been shown that an index denoting the physiological severity of a given stenosis may depend on the haemodynamic conditions under which it is measured (Siebes *et al.* 2002). Moreover, the vascular bed adapts to altered circumstances by remodelling. Studies on isolated arterioles demonstrated that a coronary microvessel undergoes structural changes in response to the haemodynamic environment and its diameter at full dilation is altered within days (Bakker *et al.* 2004). Clinical studies have shown that minimal coronary MR in a vessel treated by a stent is lower than that in a healthy reference vessel of that same patient, which suggests that outward remodelling may have taken place during the time the stenosis was present (Verhoeff *et al.* 2005). An additional complication is the existence of collateral vessels in the heart that provide pathways for blood flow from a normally perfused vessel to an area of tissue fed by a stenosed artery. It is difficult to measure collateral flow clinically and this leaves room for differences in the interpretation of pressure and flow signals in diseased coronary arteries.
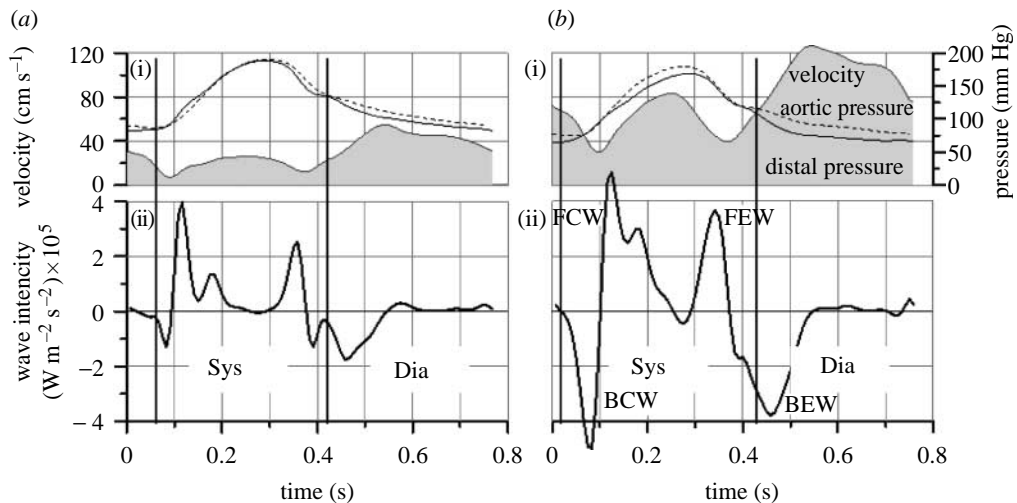
Figure 4. Pressure and flow velocity measured in a coronary artery during (a(i)) rest and (b(i)) hyperaemia. (a(ii),b(ii)) The derived signals based on WI analysis. BCW, backward compression wave; BEW, backward expansion wave; FCW, forward compression wave; FEW, forward expansion wave.

6. Dynamics of epicardial pressure and flow velocity measurements

We are only in the early stages of taking full advantage of physiological and biophysical knowledge for clinical diagnosis, since technological advancements necessary to obtain high-fidelity haemodynamic measurements in human coronary arteries have only recently become available. The currently used physiological parameters derived from the sensor-equipped guide wires are based on averages per beat and only a few studies can be found that attempt to exploit the pulsatile nature of the coronary flow and pressure signals. Because the waveforms of these signals are tightly coupled to the interaction between cardiac function and coronary perfusion, one may expect developments in decision support in the near future based on the analysis of these time-varying signals, as illustrated by the example below.

Figure 4 depicts the changes in phasic signals of epicardial pressure and flow velocity obtained in a normal coronary vessel at rest and during pharmacologically induced hyperaemia. Figure 4a(i) shows that in a normal vessel at baseline flow conditions there is almost no difference between aortic (dotted curve) and coronary pressure (continuous curve) waveforms. A small difference between aortic and coronary pressure is induced by increased flow resulting from vasodilation, especially during the high-flow diastolic period (figure 4b(i)). Adenosine increased the average coronary flow velocity approximately three times in this patient, demonstrating a sufficient coronary reserve to accommodate an increased oxygen demand during exercise.

Wave intensity (WI) analysis as introduced by Parker & Jones (1990) uses the phasic changes in coronary pressure and flow waveforms. WI is defined as the product of time derivatives of coronary pressure, P, and flow velocity, v,

$$\mathrm{WI} = \frac{\mathrm{d}P}{\mathrm{d}t} \times \frac{\mathrm{d}v}{\mathrm{d}t}.$$

WI can be interpreted as the rate of energy transported per unit area by travelling waves in the coronary vessels that are generated by cardiac contraction and relaxation at the downstream end, resulting in backward travelling waves, and by changes in aortic pressure at the inlet, resulting in forward travelling waves. WI analysis can easily distinguish between the relative contribution of backward (WI <0) and forward (WI >0) travelling waves from a single set of measurements at a site remote from where the waves are generated and it is therefore uniquely suited to study the coronary circulation. The characteristics of WI for the coronary circulation have only recently been explored in animals (Sun *et al.* 2000, 2004) and humans (Davies *et al.* 2006). The interpretation of the waves follows the biophysical analysis of the determinants of coronary perfusion outlined above.

A typical sequence of waves generated during the cardiac cycle is shown in figure 4*a*(ii),*b*(ii). The backward waves are related to cardiac contraction and relaxation when the aortic valve is closed. The first backward wave is a compression wave, backward compression wave, that originates from the microcirculation and is generated during the isovolumic contraction phase of the left ventricle and reflects the build-up of pressure while the aortic valve is still closed. The second backward wave is an expansion wave, backward expansion wave, and is caused by the relaxation of the myocardium that sucks blood back into the microvascular space.

The forward waves are related to changes in aortic pressure. The first forward wave is a compression wave, forward compression wave, and is the result of the rise in aortic pressure after the valve is opened. Apparently, the rising compressive forces in the myocardial wall during the early ejection period are not counteracting the incoming wave from the aorta. The second forward wave is an expansion wave and is the result of decreasing aortic pressure before the aortic valve closes. The vasodilation of the MR vessels induced an increase in the size of all waves without altering this characteristic pattern. Hence, WI analysis permits the investigation of coronary–ventricular interactive events throughout the heartbeat. A proper interpretation of these signals may in the near future provide a tool that can be helpful in the diagnosis of both epicardial and microvascular coronary diseases in the catheterization laboratory.

7. Future of clinical diagnosis

Much progress has been made over the past years regarding diagnostic tools and model-based interpretation of coronary signals available in the catheterization laboratory. In order to further facilitate clinical decision making with respect to CAD, it is certainly beneficial to develop better models, but we also need clinical measurements to validate these models in humans. A major breakthrough will be a more direct determination of subendocardial perfusion. Magnetic resonance imaging is a promising candidate for developing into such a method (Plein *et al.* 2007). The combined measurement of intracoronary pressure and flow velocity also yields more profitable information than that which can be obtained from either signal alone and may resolve the problem of conflicting indices by a unifying model. The behaviour of dynamic changes in stenosis severity can be studied (Siebes *et al.* 1996, 2004). The pulsatile characteristics of epicardial pressure and flow velocity signals can be used to assess the coronary microcirculation and to

better understand the ventricular–coronary interaction by employing more sophisticated model-based analysis. Proper interpretation of the information obtained from intracoronary haemodynamic signals and measurements of perfusion distribution requires realistic models of the coronary circulation, based on knowledge about the detailed anatomical structure of the coronary microcirculation, cardiac function and mechanisms of interaction between cardiac contraction and coronary flow. The VPH project provides a promising framework in which to develop this work. The coronary circulation is a complex system for which an integrated VPH approach is likely to yield significant advancements with a direct benefit for improved diagnosis and treatment of CAD in patients.

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