Improved assessment of functional severity of coronary artery stenosis by analysis of combined intracoronary pressure and flow velocity signals

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Chapter 2
Myocardial perfusion distribution and coronary arterial pressure and flow signals: clinical relevance in relation to multiscale modeling, a review

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Abstract

Coronary artery disease (CAD) is associated with both narrowing of the epicardial coronary arteries and microvascular disease, thereby limiting coronary flow and myocardial perfusion. CAD accounts for almost 2 million deaths within the EU on an annual basis. In this paper we review the physiological and pathophysiological processes underlying clinical decision making in coronary disease as well as the models for interpretation of the underlying physiological mechanisms. Presently, clinical decision making is based on non-invasive magnetic resonance imaging (MRI) of myocardial perfusion and invasive coronary hemodynamic measurements of coronary pressure and flow velocity signals obtained during catheterization. Within the euHeart project several innovations have been developed and applied to improve diagnosis based understanding of the underlying biophysical processes. Specifically MRI perfusion data interpretation has been advanced by the transientogram, for hemodynamic data functional indices of coronary stenosis severity that do not depend on maximal vasodilation are proposed and the Valsalva maneuver for indicating the extravascular resistance component of the coronary circulation has been introduced. Complementary to these advances, model innovation has been directed to the porous elastic model coupled to a one dimensional model of the epicardial arteries. The importance of model development is related to the integration of information from different modalities which in isolation often result in conflicting treatment recommendations.
Introduction

Coronary artery disease (CAD), accounts for almost 2 million deaths within the EU on an annual basis. It is associated with an annual mortality rate of 25% once congestive heart failure develops (65). Cardiovascular disease often leads to focal narrowing of epicardial arteries, limiting coronary flow and myocardial perfusion. The resulting myocardial ischemia is not only secondary to epicardial disease, but also caused by alterations at the microvascular level. In general, myocardial ischemia is not global, but shows heterogeneity. Subendocardial layers are more vulnerable to ischemia than the subepicardial layers as a consequence of the compression of the embedded vasculature (12, 33, 34). The structure of the coronary vascular network seems to be designed to compensate for this subendocardial impediment by a large volume of subendocardial resistance vessels (106). This results in a layer-specific distribution of resistance in the diastolic state (15, 26). The impeding effect of contraction on microvascular flow is the result of several mechanisms including local tissue pressure and muscle stiffness (48, 94, 103) and this effect is altered in the presence of an epicardial stenosis (60). Hence, myocardial perfusion in the presence of CAD is complicated, and its analysis requires insight in mechanisms determining perfusion at a local level, and its translation into the morphology of coronary pressure and flow signals.

The increase in computational power facilitates analyses of large and diverse sets of biological data by means of multiscale biophysical modeling of organ function (36, 66) which generally encompasses the interaction of different physics such as fluid dynamics and large-deformation mechanics. Within the context of CAD, computer simulations may help to understand the flow and perfusion alterations secondary to atherosclerosis (52). Moreover, such models may find direct clinical application in diagnosis and treatment of patients with CAD by offering a biophysical interpretation of perfusion distribution patterns in relation to hemodynamic parameters derived from coronary arterial pressure and flow signals. Within euHeart, the CAD work package aimed at developing a comprehensive model of the coronary circulation starting from detailed knowledge of the coronary arterial tree morphology embedded in a mechanical model of the contracting myocardium. Moreover, clinical data was obtained on perfusion distribution by perfusion magnetic resonance imaging (MRI), as well as on coronary hemodynamics derived from epicardial pressure and flow velocity signals.

This paper reviews the literature on the application of perfusion models of the heart as well as physiological knowledge in order to provide a comprehensive assessment of the state of the art, especially in relation to clinical applicability. However, it will start out with a description of the pathophysiology of CAD and its treatment. Throughout, specific results obtained within the euHeart project are illustrated in order to underline the relevance of specific models to clinical applicability.
Clinical and physiological background

Revascularization therapy of CAD started some 50 years ago and its development has recently been described (30). Initial treatment involved bypass surgery requiring the opening of the thorax and use of a heart-lung machine. In such a procedure, either an internal mammary artery or a vein harvested from the leg was used to connect the coronary artery distal of the stenosis to the aorta. Presently, the treatment of choice is percutaneous coronary intervention (PCI). In this scenario, a peripheral artery is made accessible using an introduction sheath through which a guiding catheter is introduced (lumen diameter varying between 5 and 7F (1F=0.3 mm)) that is advanced to the ostium of either the left or right coronary artery. A guidewire (diameter~0.014 inch) with a flexible tip is advanced through the guiding catheter and maneuvered distal to the stenosis. The epicardial narrowing is, in general, treated by predilation using an expandable balloon followed by stent placement. Special guide wires have been developed equipped with a pressure and/or flow velocity sensor at its tip to obtain intracoronary hemodynamic signals (82). These signals allow an evaluation of the functional significance of a stenosis in terms of pressure and flow velocity alterations.

Coronary pressure and flow velocity signals

Flow velocity as measured by a Doppler crystal is the maximal velocity detected by the Doppler signal in a cross section of the vessel a few millimeters away of the sensor from which average velocity and eventually flow can be calculated when vessel diameter is known (24). However, maximal flow velocity is used in clinical studies and in this paper throughout. Because of the small diameter, the guide wire has only an influence at narrow stenoses (98). The intracoronary hemodynamic signals obtained from a coronary artery before and after stent placement for the same patient are demonstrated in Figure 1. The signals after stent placement, indicated as “POST” in the figure, approximate a normal physiological condition and will be discussed as such. The figure depicts the coronary flow velocity signal rather than coronary flow but for practicality, proportionality between these two physically different quantities will be assumed in discussing the physiology of coronary flow and the effect of a coronary stenosis on it.

Normally, coronary flow is pulsatile as a result of the effect of heart contraction on intramural vessels which will be discussed in more detail in relation to Figure 3. Flow is still pulsatile in the presence of a stenosis as is clear from the left side of the figure indicated by “PRE”, but in general the amplitude of flow pulsations decrease with increasing stenosis severity. Nutritious flow is related to the beat average flow which can vary fourfold between resting conditions and exercise in a normal heart. The ratio between maximal flow and flow at rest is denoted as coronary flow reserve (CFR) and in case of flow velocity by coronary flow velocity reserve (CFVR). In Figure 1, the effect of exercise is mimicked by an intracoronary bolus injection of adenosine.

1 Data from patients presented in this paper were obtained from study protocols approved by the Medical Ethics Committees of the AMC and KCL, and all patients gave written informed consent.
Figure 1: Hemodynamic measurements recorded with a dual-sensor-equipped guide wire obtained in a diseased vessel distal of an 85% diameter narrowing (PRE) on the left and after treatment (POST) at the same measurement location on the right. At the arrows an intracoronary bolus of adenosine was injected to test the dilatory capacity of the coronary circulation. It is clear that when a stenosis is present, the ability of the coronary circulation to increase flow when needed, e.g. in case of exercise, is reduced. The artificially high increase in the aortic pressure signal is due to the bolus injection of adenosine through the same line by which aortic pressure is obtained. CFVR, coronary flow velocity reserve; FFR, fractional flow reserve; HSR, hyperemic stenosis resistance; ΔP, stenosis pressure gradient; Pa, aortic pressure; Pd, distal pressure.

Figure 2: Pressure gradient-flow velocity relationships prior to (pre) and after (post) stent placement and for a reference vessel (ref) in one specific patient. ΔP, pressure gradient; v, velocity.
dilating all resistance vessels in the heart and CFVR was increased over twofold by treatment. The reduced CFVR in the presence of a stenosis clearly demonstrates the impeding effect of such a narrowing on coronary reserve, and the latter CFVR increase is indicative of a successful treatment.

Nutritious coronary flow is adapted to tissue oxygen usage which depends on the cardiac work load and is related to the oxygen needs of the body as a whole. This process of adaptation of blood flow to cardiac oxygen usage is denoted as metabolic regulation. In case of reduced coronary pressure, such as in the presence of a stenosis, beat average coronary flow is still matched to oxygen consumption although not perfectly. This relative constancy of coronary flow at constant oxygen consumption in the face of coronary pressure changes is denoted as autoregulation. These regulatory actions related to metabolic and auto-regulation are mediated by the smooth muscle tone in the vascular walls of small arteries and arterioles which are generally referred to as resistance vessels.

The presence of a stenosis interplays with these regulatory processes for coronary flow. In our example the beat average pressure distal of the stenosis (Pd) is reduced by about 25 mmHg at rest, whereby the effect on flow is compensated for by autoregulation. However, the pressure drop increases with flow in response to an increased metabolic demand, mimicked by adenosine, as is clear from the bottom panel in Figure 1. This further limits the maximal obtainable flow. Since autoregulation and metabolic regulation both act via the smooth muscle tone in resistance vessels, these processes are not independent. Tone in the resistance vessels is reduced by autoregulatory response to the stenosis-induced pressure drop: first at rest, then further by the increase in stenosis pressure drop when flow is increased by exercise. Hence the regulatory capacity for metabolic regulation is reduced by the stenosis pressure drop. When flow cannot meet the metabolic demand, ischemia is induced.

The hemodynamic effect of a coronary artery stenosis is uniquely characterized by the pressure gradient-flow velocity (ΔP-v) relationship as is illustrated in Figure 2. Such a relationship can be obtained from the transient change in flow velocity following the injection of adenosine such as demonstrated in Figure 1 for a target vessel prior to and after treatment of the stenosis and for a reference vessel in the same heart (Figure 2). After treatment (post), the curve alters such that pressure drop at the same velocity is diminished and the obtainable range of velocity has increased and the resulting hyperemic pressure drop has decreased.

As is demonstrated in Figure 2, the ΔP-v relationship becomes less curvilinear with decreasing stenosis severity, and is linear for a non-stenotic reference vessel. A ΔP-v relationship follows the quadratic function of ΔP = A·v+B·v^2, where the coefficient A represents the viscous pressure losses through the narrowed vessel due to the increased flow velocity and B the exit losses beyond the stenosis. Although the relationship is stenosis specific (28, 107), the range of flow velocity and pressure gradient covered by a measured curve depends on the degree of reduction in microvascular resistance (MR).
The total resistance in the interrogated vascular bed is derived from the ratio between aortic pressure and flow velocity. Since stenosis resistance (SR) and MR are in series, and SR is known, MR can be calculated (81). Assuming that MR remains unaffected by the alteration in stenosis properties, the increase in maximal velocity obtainable by treating the stenosis can then be predicted for the reduction in SR. These predicted maximal flow velocity is indicated by the arrow in Figure 2. However, the obtainable increase in flow velocity exceeds this prediction and one has to conclude that hyperemic microvascular resistance (HMR) is decreased after treatment of the stenosis. An explanation for this decrease in HMR is that the resistance vessels are further dilated passively (which is in contrast to changing vessel wall tone) by the increasing perfusion pressure, a direct result of the distensibility of these vessels. An alternative explanation could be the decrease of collateral flow, which enters the interrogated vessel distal to the location of the velocity measurement (1). However, this collateral effect disappears when hyperemic pressure drop over the stenosis is reduced (100). Since the maximal level of flow velocity increases consistently with further reduction in stenosis severity, the collateral flow seems not to be the major role and the reduction in MR forms the better explanation (100).

The ΔP-v relationship for the reference vessel demonstrates that there is only a very limited pressure drop in coronary epicardial arteries in normal vessels also at vasodilatation. In Figure 2 the lower level of maximal obtainable flow velocity in the reference vessel compared to the treated vessel may be caused by a higher MR in the tissue perfused by the reference vessel than MR in the tissue perfused by the target vessel after treatment. This may be the result of natural variation in MR as discussed below. Indeed, it is a consistent finding that HMR in the treated vascular

![Figure 3: Hemodynamic signals (A) and net wave intensity (B) during a single cardiac cycle at rest in a reference vessel (left circumflex coronary artery). BCW, backward compression wave; BEW, backward expansion wave; dI, net wave intensity; FCW, forward compression wave; FEW, forward expansion wave; Pa, aortic pressure; Pd, distal pressure; P lv, left ventricular pressure.](image-url)
bed after treatment is lower than that in the vascular bed perfused by the reference vessel at the same pressure, which can be the result from outward remodeling of the resistance vessels as a consequence of the long period of low perfusion pressure distal of the stenosis (99).

**Interaction between heart contraction and coronary circulation**

The interaction between cardiac muscle and the intramural vasculature results in the typical intracoronary flow velocity profile for non-obstructed branches of the left coronary arteries as depicted in Figure 3A, where coronary flow velocity is higher in diastole than in systole, and out of phase with coronary arterial pressure, which is highest in systole. Decreased systolic flow is due to the squeezing of cardiac muscle on embedded intramural vessels which impedes arterial inflow and augments venous outflow. During muscle relaxation the intramural blood volume is restored, causing an increased inflow and reduced outflow. This squeezing effect is denoted as intramyocardial pump mechanism (88).

In addition to the global systolic-diastolic differences, further insight into the underlying mechanisms can be derived from the coronary pressure and flow velocity signals. Flow velocity starts to decrease in the isovolumetric contraction phase of early systole which corresponds to the rise in left ventricular pressure \( P_{LV} \) squeezing the intramural vessels. At the moment \( P_{LV} \) rises above the aortic pressure, the aortic valve opens, and coronary arterial pressure increases, opposing the pressure generated in the intramural vessels, maintaining coronary flow at a systolic level. During relaxation of the left ventricle (LV) intramural pressure in the LV wall decreases, thereby facilitating an increase in coronary inflow. After full dissipation of the pressure in the LV, the myocardial wall is relaxed and coronary flow decreases concomitantly with the diastolic fall in aortic pressure.

The series of events within a cardiac cycle are well illustrated by wave intensity analysis (WIA) as is illustrated in Figure 3B. WIA is a time domain analysis of traveling wavefronts, which distinguishes between contributions originating from upstream and downstream events (8, 71). It is uniquely suited to investigate the coronary circulation, where forward waves arise from the aorta and backward waves originate in the small vessels within the contracting or relaxing myocardium. Wave intensity \( (\text{dI}) \) is defined as the product of incremental changes in local pressure \( (\text{dP}) \) and flow velocity \( (\text{dU}) \). Coincident forward \( (\text{dI}^+ \) and backward \( (\text{dI}^- \) travelling waves are superimposed to form the net wave intensity at the measurement location (69, 70). Net wave intensity \( (\text{in } \text{W/m}^2\text{s}^2) \) is calculated and normalized for the sampling rate by \( \text{dI} = \text{dP}/\text{dt} - \text{dU}/\text{dt} \). With the use of the wave speed of traveling waves, the separate forward and backward contributions to the total net wave intensity can be calculated as \( \text{dI}_{\pm} = 1/4 \cdot \rho \cdot c \cdot (\text{dP}/\text{dt} \pm \rho \cdot c \cdot \text{dU}/\text{dt})^2 \), where \( \rho \) is the blood density \( (1060 \text{ kg/m}^3) \) and \( c \) is the wave speed \( (\text{in } \text{m/s}) \) determined by the single-point technique (21). The energy \( (\text{in } \text{J/m}^2\text{s}^2) \) carried by each wave is quantified by integrating the area under each of the separated dominant waves.
In a coronary artery, four net main waves can be distinguished in a cardiac cycle, based on their direction and their effect on pressure and flow as illustrated in Figure 3B. Compression waves increase pressure while expansion waves decrease pressure. At the start of a cardiac cycle, a backward compression wave (BCW) propagates from the microcirculation due to the compression of the intramural vessels during the isovolumetric contraction of the LV. After opening of the aortic valve, this wave is followed by a forward traveling compression wave (FCW) due to the continuing increment in aortic pressure. In turn, this wave is followed by a forward traveling expansion wave (FEW) which is the result of the decrease in the aortic pressure due to the start of the LV relaxation. After closure of the aortic valve, when LV relaxation continues and the aortic pressure further decreases due to the reduction in compression of the intramural vessels, a backward traveling expansion wave (BEW) is dominant.

Within the euHeart project we demonstrated the potential of WIA during the Valsalva maneuver, expiration against an obstructed glottis, to quantify the compression effect of heart contraction on the microvascular resistance (77). During this maneuver, coronary flow increased despite a decrease in coronary pressure gradient, which can be attributed to reduction in extravascular resistance.

The effect of cardiac contraction is especially noticeable from the distribution of coronary flow over the heart muscle, which will be discussed in more detail later.

**Clinical indices for physiological significance of a coronary stenosis**

From the discussion on ΔP-v relationships for stenoses, it would be logical to quantify the stenosis severity by the characteristics of these curves. However, the feasibility of this measurement is rather recent (82), and alternative clinical methods have been introduced based on pressure or flow velocity alone. In this section, some clinical indices of the physiological significance of coronary stenoses will be discussed. These indices are mostly based on the beat average values of aortic pressure and pressure distal of the stenosis or coronary flow velocity.

**Coronary flow velocity reserve**

The physiological meaning of CFVR has been discussed above in relation to Figure 1. CFVR is obtained clinically by measuring flow velocity before and during adenosine induced vasodilatation. In healthy hearts, CFVR values as high as 4.5 have been reported (49). Epidemiological studies have indicated that a stenosis should be treated when CFVR is lower than 2 (50).

**Fractional flow reserve**

SR is in series with MR, and hence, the ratio between distal and aortic pressure, Pd/Pa, equals MR/(MR+SR) (81). Obviously, this is only true when venous pressure is zero. In general, this value is around 5 mmHg and neglected for practical purposes. Hence, the limitation that a stenosis poses on coronary flow at maximal vasodilatation, when MR is minimal, can be expressed by Pd/Pa at hyperemia and
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is generally referred to as fractional flow reserve (FFR). Assuming that SR and MR at maximal hyperemia are pressure and flow independent and HMR is equal in the absence and presence of the stenosis, FFR indicates the stenosis induced reduction in hyperemic flow (75). In unstenosed vessels, FFR equals 1. A threshold of 0.75 was found as indicative of reversible ischemia by independent methods such as single photon emission computed tomography (SPECT). More recently, a cut-off value of 0.8 is used in clinical practice (104).

Hyperemic stenosis resistance
The ratio of stenosis pressure gradient to distally measured flow velocity can be interpreted as a velocity-based resistance index. Please note that the units of a velocity-based resistance index are different from those of a flow-based resistance. At maximal hyperemia, this resistance is denoted as the hyperemic stenosis resistance (HSR). HSR has been shown to be more stenosis specific than CFVR and FFR (62) since it is almost independent on HMR, which depends on a variety of clinical and hemodynamic factors. It has been demonstrated that approximately 30% of patients with an angiographically determined intermediate stenosis severity show discordant outcomes between CFVR and FFR (61). HSR has been validated as a predictive index for reversible ischemia by SPECT as well and was shown to be superior to FFR and CFVR, especially for those patients with discordant outcomes between the latter two indices. A threshold for reversible ischemia of 0.8 mmHg/cm/s was found (62).

Clinical indices of functional stenosis severity not requiring maximal hyperemia
The aforementioned indices all require maximal hyperemia, although HSR to a smaller extent since the pressure gradient is divided by the flow velocity and both parameters alter in the same direction with vasodilation (62, 74, 92). Most frequently, adenosine is used to induce hyperemia (59). However, adenosine is not always available in the catheterization room in an applicable form due to local regulatory issues. This may in part explain that functional assessment of stenosis severity is performed in the USA in only about 6% of the patients undergoing diagnostic cardiac catheterization. Therefore, several alternative indices of functional stenosis severity have been proposed that do not require the achievement of maximal vasodilatation.

The diastolic stenosis pressure gradient at a fixed flow velocity of 50 cm/s (dP_{v50}) can be derived from the diastolic ∆P-v relationship and does not need maximal hyperemia (56, 57). More recently, two drug-free indices have been introduced, namely the instantaneous wave-free ratio (iFR) (79), which is based on the distal-to-proximal pressure ratio during a specific mid-diastolic period, and baseline stenosis resistance (BSR), calculated as the ratio between the stenosis pressure gradient and distally assessed flow velocity under basal conditions (93). Both iFR and BSR can be obtained during resting conditions. BSR is one of the outcomes of the euHeart project.
Clinical assessment of perfusion distribution

Rationale for non-invasive measurement of perfusion

Perfusion of the myocardium is heterogeneous, which is not only induced by flow hindrance in one of the sub-branches, but also due to nonsymmetrical branching of the coronary arterial tree (7, 52) and regional differences in function (4). Especially during hyperemia, regional differences across the layers of the myocardium result from spatial variation in the intramural compressive forces (6). The hemodynamic conductance at the subendocardium diminishes with diastolic time fraction with perfusion pressure as a parameter (26). Thus, because of perfusion heterogeneity, the hemodynamic parameters measured at the epicardial arteries may appear to be normal in the presence of local ischemia.

Since myocardial ischemia is more pronounced in the subendocardial layers of the LV (2, 26, 90), non-invasive assessment of myocardial perfusion is becoming essential in treatment decision making for an increasing number of patients with stable CAD. Event-free survival can be improved when decisions regarding revascularization are based on the presence of ischemia (22, 73, 91). Cardiac magnetic resonance (CMR) perfusion imaging is increasingly used to diagnose non-invasively the presence of CAD and to document the presence of myocardial ischemia for clinical decision making (10). The main advantages of CMR perfusion imaging is the lack of radiation exposure as with computed tomography (CT) (5), the excellent safety profile of the contrast agents and the capability of CMR perfusion imaging to provide dynamic images of myocardial perfusion with a better spatial resolution compared with other imaging modalities (42). After extensive validation against microspheres (18, 35, 105) and invasive reference standards like FFR (20, 55 102), CMR perfusion imaging is becoming the non-invasive test of choice in patients with stable CAD, at least equivalent to results of SPECT (31).

Figure 4: Transmural perfusion gradient (TPG) analysis (modified with permission from the publisher). (A) Single image from a CMR perfusion image series. (B) Bull’s eye plot of the peak perfusion gradient. (C) Example of mid-myocardial perfusogram (gradient as function of angle and time). (D) Thresholded perfusogram indicating potentially ischemic areas in green.
Moreover, the excellent spatial and temporal resolutions are interesting features of CMR perfusion imaging. As such, this technique allows to obtain separate information from the endo- and the epicardium (55, 68, 76), and therefore, CMR perfusion imaging is highly attractive for clinical and research purposes.

CMR perfusion imaging also has drawbacks compared with other modalities. Image acquisition still takes considerable longer modalities (typically 30–45 min), and the production of high-quality images requires experienced, specially trained magnetic resonance imaging (MRI) operators. Furthermore, CMR perfusion imaging cannot be used for patients with pacemakers or claustrophobia. The use of contrast-enhanced CMR perfusion imaging needs to be weighed against other risks for patient with renal insufficiency due to a small risk of nephrogenic systemic fibrosis.

**Analysis of high-resolution cardiac magnetic resonance perfusion imaging**

Clinically, CMR perfusion images are usually interpreted based on visual assessment. Expert observers integrate the spatial and temporal information of the contrast agent arrival in the myocardium into a coherent account, using typical patterns as diagnostic markers. Besides the requirement of significant training of the highly specialized observers, a limitation of visual assessment is its inability to identify the presence of balanced ischemia in patients with three-vessel disease. In balanced ischemia, there is no normal reference segment, and as such, relative abnormalities can be missed (72). Quantitative analyses may be able to overcome these shortcomings and also provide additional information based on the abundance of data contained in the CMR perfusion images (42, 44, 45).

Using standardized methods (e.g., specific contrast agent injection schemes (43), model-independent deconvolution (44)) myocardial perfusion reserve (MPR) can be assessed objectively (72) in a reproducible manner (64). This has been validated against microspheres (18) and FFR (55). We have recently shown comparable quantitative results of CMR-MPR with positron emission computed tomography (PET) (76).

We have now expanded these techniques within euHeart to differentiate blood flow on a voxelwise level, thus discriminating the endo- and epicardial layers to better understand the (patho-)physiology and to improve sensitivity of disease detection. To achieve this, we have developed a novel hardware CMR perfusion phantom (16) to validate our techniques for voxelwise quantification (108) in comparison with microspheres and animal data, as well as translated novel high-resolution imaging techniques (35) into patient studies. Voxelwise quantitative analysis allows the quantification of MPR while preserving the information about extent, localization and transmurality of ischemia (ischemic burden). Combining the advantages of visual (high spatial resolution) and quantitative (more objective and reproducible) assessment, voxelwise quantification has the potential to allow an improvement in the accuracy of detection of CAD as well as to provide novel and valuable information on the severity and extent of ischemia.
An alternative pathway is transmural perfusion gradient (TPG), which assesses the perfusion gradient between the endo- and epicardium as depicted in Figure 4. This method is highly attractive due to several advantages. As the difference between epicardial and endocardial perfusion is measured, the method autocorrects for differences in contrast agent injection schemes, CMR data acquisition methods and coil sensitivities. It does not require a specific pre-bolus as no input function is used. In addition, it can be evaluated from stress scans only. As such, it can be applied in many standard clinical scenarios. TPG analysis is based on a two-dimensional ‘gradientogram’, which displays the evolution of the transmural gradient in LV myocardial perfusion (contrast uptake) over time. Using the temporal persistence and radial extent of a perfusion gradient, normal perfusion and areas of reversible ischemia can be differentiated with excellent accuracy (32). We have recently optimized and validated the diagnostic criteria for TPG in patients with suspected CAD versus FFR (17). With TPG analysis, we achieved a comparable diagnostic accuracy as visual assessment in a fully automated fashion.

Complementary nature of clinical indices

Hemodynamic indices are not always consistent in their recommendation to treat a vessel. For example, as mentioned previously, FFR and CFVR are not consistent in approximately 30% of coronary lesions (61). Also MRI and FFR do not perfectly match. To demonstrate the difficulties in diagnosing coronary disease, we examine a patient case, for which the MRI perfusion is depicted in Figure 5. Panel A demonstrates hypoperfusion of the inferior and lateral wall supplied by the right coronary artery compared to the septum prior to treatment, which is most pronounced in the endocardium. Perfusion is normalized after treatment of the stenosis (panel B). This case is interesting since the patient was originally diagnosed by angiography as having three-vessel disease and as such was a candidate for bypass surgery. After functional measurements with MR and FFR of the different lesions, the patient was regarded with single-vessel disease and treated by a stent via PCI. However, the lesion treated resulted pre-PCI in the following indices: FFR=0.78, HSR=1.4 mmHg/cm/s, CFVR=1.9. Based on the FFR threshold of 0.75 the stenosis would not induce ischemia, but based on HSR (threshold 0.8) and CFVR (threshold 2.0) it should. Although the most important conclusion is that surgery was avoided, the physiological results for this patient point to the differences of different parameters as each parameter relies
on numerous assumptions. Such findings underline the importance for a realistic biophysical model unifying all aspects of coronary physiology.

**Model development of the coronary circulation**

For a proper interpretation of clinical measurements in terms of hemodynamics and perfusion distribution, models of the coronary circulation are required that capture the structure of the coronary tree, the physiological mechanisms of distensibility of vessels in hyperemic conditions and the intramural compressive forces that impede perfusion at a regional level. Attempts have been made in the past applying lumped models where vessel compartments have been approximated by either linear or non-linear resistances and compliances (3, 6, 11). With the availability of increasingly high-resolution information revealing the structure of the intramural coronary arterial tree (46, 47, 96), more detailed models have been presented (37, 38, 86). However, since the morphological data were obtained from corrosion casts, the 3D information about location and orientation of the coronary vessel segments was lost. With the recent possibilities to measure vascular structure by CT for smaller hearts and by the imaging cryomicrotome (95) for larger hearts the 3D structure of the coronary arterial tree can now be retained. These anatomically accurate tree representations, in combination with increasing computational power, provide the means to develop more realistic coronary models.

**Coupled Navier-Stokes blood flow models**

Coronary blood flow is divided across many scales. The diameter of the epicardial coronary arteries is in the order of $3 \times 10^{-3}$ m whereas the diameter of a capillary is in the order of $7 \times 10^{-6}$ m. Blood flow in the larger vessels can generate complex secondary flow patterns at vessel curves and bifurcations. Flow analysis is further complicated by the compliance of the vessel wall. 3D Navier-Stokes models on deforming domains can be employed to resolve the flow in such individual vessels (25). In the smaller vessels with lower Reynolds numbers, flow patterns are less complex, but their branching structure leads to far more segments with decreased diameters. Thus the computational cost of applying 3D models to all vessel segments in the coronary arterial system would make such an approach intractable. In this context, 1D models seem better suited for investigation of unsteady blood flow. 1D network models have been developed for many years for the systemic circulation (4) and have been developed more recently for the coronary circulation as well. These models approximate the blood vessel as a one-dimensional elastic tube and describe the conservation of mass and momentum in the space-time domain. Various recent numerical studies have demonstrated the computational tractability of the 1D approach (54, 80, 85), which comes at the cost of only providing information averaged over the vessel cross-section. These studies have a common root in a basic underlying mathematical model that dates back to the 18th century, proposed by Euler. The focus of more recent work has been to achieve an efficient computational solution of the governing equations, using both finite difference (84) and finite element techniques (27), including high-order spectral element method implementations (80). These modeling frameworks have in turn enabled investigations into coronary blood flow dynamics ranging in scale from hematocrit distribution (53) through to
the whole organ effects of heart rate on systolic flow impediment (26). 1D blood flow models provide a reasonable description of the propagation of pressure waves in arteries, and they have also been used to investigate the effects on pulse waves of geometrical and mechanical arterial modifications, e.g., flow alteration due to a stenosis, or treatment by PCI (80). A central challenge with translating these models into clinical applications is their dependence on detailed anatomical information which is typically not available via in vivo imaging of human subjects. This motivates development of the alternative approaches discussed below.

Solutions to both 1D and 3D systems of blood flow are highly dependent on the boundary conditions imposed to represent the vessels distal to the simulated domain. However, it is frequently the case that the flow distribution and/or pressure field at the simulated domain boundaries is unknown and is difficult, if not impossible, to determine experimentally. Thus, it is noteworthy that some 1D blood flow studies (27, 80, 84) attempt to overcome this boundary condition issue by extending their model to couple the terminal points of the discrete vessel network to lumped parameter models (2). These extended models allow for flow in a network to be calculated while taking into account distal resistances not explicitly represented by discrete vessels. The development of these terminal resistance-type phenomenological models was based in part on the intramyocardial pump theory of Spaan et al. (88).

In some cases only lumped-parameter models have been used to completely reproduce the observed flow responses to arteriolar and venular pressures of an anatomically based model combining nonlinear resistive and capacitive elements (11). This is a reasonable, computationally efficient way of reproducing experimentally observed behavior while maintaining some of the fundamental physics of the problem. However, the treatment of vascular subgroups as single entities whose behavior is assumed to be characterized by a small number of parameters may be deemed to be somewhat crude for certain modeling applications. For example, a lumped-parameter component is of limited use for modeling (as discussed above) many of the inherently heterogeneous phenomena, e.g., local metabolite delivery and interpretation or prediction of contrast MRI results where fine spatial detail is required.

3D tissue perfusion models
For the reasons outlined above, a comprehensive model of perfusion necessitates the spatial treatment of the microcirculation, that is, not simply using lumped parameters. Moreover, the main clinical interest is often focused on regional perfusion states (e.g., the American Heart Association standardized myocardial segmentation), typically expressed in terms of capillary pressure and flow. Therefore, a continuum approach to blood perfusion, describing blood flow throughout the perfused domain by averaged quantities, would be appropriate. This point is further reinforced by the fact that clinical perfusion data, provided by PET, SPECT or MRI, are inherently spatially averaged, thereby enabling continuum perfusion models, with a spatial scale directly matched to the relevant imaging resolution, to be directly compared with imaging data in comparison to alternative discrete perfusion models.
Exploiting this approach, some continuum models, developed via homogenization theory, have been successfully utilized for studying the mechanics of perfused myocardium (58). In these models, homogenization theory is used to extract effective or macroscale parameters for heterogeneous media from more elaborate microscopic models. Homogenization of periodic media has previously been employed in a 3D model of fluid flow and transport within both healthy tissue and tumor regions (14). Despite providing an elegant method of separating flow at the various vessel scales under consideration, this theory does require the existence of a repeating unit or periodic “canonical cell”. As biological arterial networks are generally aperiodic in nature, a method of parameter derivation that does not require periodic vascular features is desirable.

The multicompartment porous model of Huyghe et al. (40) allows for scale separation of the flow and does not require any periodicity of the material properties. In this model, fluid flows through compartments of decreasing arterial radius, into a capillary compartment, and is then drained via compartments of increasing venous radius. The sequential flow amongst compartments is an assumption that greatly simplifies the model and is representative of an underlying idealized network, although no actual discrete network is referenced. Due to the lack of a vascular model, their approach to parameterize the permeability tensor field was to assume isotropic tensors, proportional to the square of the intramyocardial blood volume under a constant vessel length assumption.

The 3D perfusion models mentioned thus far lack the ability to capture fluid-solid interactions (67, 83). In Huyghe et al. (39), the authors applied a mixture theory model to the mechanics of the left ventricular myocardium. Their two-phase mixture model featured a solid component and a fluid component. It allowed for finite deformation of the tissue and was fundamentally based upon the work of Biot (7) and Bowen (9). As their model consists of a single porous domain, the authors admit to not being able to model physiological coronary blood flow, in the sense of a flow from arteries to veins. More recently, Chapelle et al. (13) presented a derivation of a general single-compartment poroelastic model valid for a nearly incompressible medium which experiences finite deformations and features active contraction, fibre orientation and spatially distributed volumetric fluid influx. It was sufficient to reproduce some known mechanical effects resulting from the mechanisms of crosstalk between the myocardium and coronary flow, such as a decrease in myocardial volume, flow impediment during contraction and a nonlinear transmural pressure field. While this paper represents a significant contribution to the model development of cardiac perfusion, it too applied an unphysiological isotropic permeability tensor field. Interestingly, the lack of an explicit representation of the arterial and venous vessels is flagged by the authors as a major limitation of their model, a factor which is blamed upon a lack of sufficiently detailed measurements to both parameterize and validate the model.
**Figure 6:** (A) Vascular model derived from a porcine cryomicrotome data set. This model has been reduced to the available vessels that perfuse the LV tissue model only. Red vessels represent the 1D model component, silver vessels represent the remaining vessels that are utilized in the parameterization process. (B) The derived permeability tensor field with glyphs directed along the principal eigenvector and colored according to the normalized principal eigenvalue. (C) The Darcy pressure solution.

**Figure 7:** (A) The cross-sectional area of the feeding artery of the red subtree was decreased by a factor of 0.7 to model stenosis of a branch of the coronary artery. (B) Total concentration of contrast agent in the tissue 20 s after administering a bolus injection for a physiologic case. (C) The simulated occlusion of a coronary artery branch.
Parameterization of 3D perfusion models from discrete vascular models

A more physiologically realistic model of perfusion in biological tissues with an embedded vasculature was undertaken by Vankan et al. (97). This was also a multi-compartment perfusion model, accompanied by an explicit synthetic network created using a constrained constructive optimization algorithm (78). A spatial averaging technique, utilizing a moving averaging window, was used to derive the permeability fields for each Darcy compartment, and the intercompartment coupling terms. This technique was derived in Huyghe and van Campen (41) and makes use of the Slattery-Whitaker spatial averaging theorem. Although derived for a 4D Darcy model, whereby the fourth dimension allowed for volume coupling between neighboring 3D porous compartments, perhaps because of computational limitations at that time, Vankan et al. only simulated 2D porous domains. This model, while pioneering, neglected the connections across non-neighboring compartments identified by histological studies showing cross-Strahler ordering connectivity (46). Despite the decrease in the number of connections with compartment separation order, the fact that the pressure difference simultaneously increases means that these long-range intercompartmental effects could be quite significant. This cross-Strahler ordering, or non-neighboring porous compartment connectivity, is a feature of anatomical vascular models that is not captured by the synthetic networks used by Huyghe and Vankan.

Most recently, Cookson et al. (19) produced a 3D multi-compartment perfusion model of a porcine LV free wall segment. The Darcy compartments of this perfused tissue region were parameterized using an arterial vascular model derived from cryomicrotome data (89, 95) which was also used to define the region boundary itself. These authors demonstrated that there is a significant improvement in the Darcy pressure (with respect to a comparison to the associated spatially averaged Poiseuille pressure) when the non-neighboring connections are accounted for. In the same work, their perfusion model was then extended into a poroelastic framework. The combination of having the Darcy model parameters determined from anatomically realistic vascular models, and the poroelastic simulations being carried out on a cardiac geometry constructed from the same cryomicrotome data set, arguably constitutes an ideal in silico framework for studying the effects of fluid-solid coupling on the coronary perfusion state. Such mechanical coupling is widely thought to be of critical importance to cardiac function and, in particular, to have a large impact on the coronary circulation (48, 103).

The modeling framework just described, and shown in Figure 6, provides the capacity to run clinically relevant simulations where ischemia results from vessel occlusion. This is shown in Figure 7, where a simulation of perfusion in the myocardial tissue of a porcine LV was performed using the 3D-compartment Darcy model coupled to a 1D flow model based on the incompressible Navier-Stokes equation in an elastic vessel. The geometry is derived from cryomicrotome data of the coronary vasculature (29). While arteries with a diameter larger than 0.22 mm are represented as a discrete tree, all arteries of smaller size, arterioles and capillaries are modeled as a homogenized Darcy model of three distinct yet spatially coexisting compartments that exchange
fluid mass. The venous system is represented via a pressure dependent sink term in compartment three.

To simulate the stenosis of a coronary artery branch, we decreased the cross-sectional area of the branch feeding the hypoperfused region displayed in Figure 7A by a factor of 0.7. To enable the direct comparison of simulation results with clinically acquired images, transport of the contrast agent, as used in MR perfusion imaging, was modeled using a multicompartment system of reaction-advection-diffusion equations. This model accounts for both the transport in the blood, for each of the porous compartments, and the diffusion of contrast agent through the capillary wall into the extracellular space. The observed concentration which is a proxy for the MR signal is therefore the porosity-weighted sum of each of these component concentrations. Figure 7B and 7C show a contour plot of the total concentration for both a healthy and diseased case, 20 s after the injection of the contrast agent bolus. Although both sets of results display spatial inhomogeneity, in the pathological case there is a large region of near-zero concentration indicating that the contrast agent has not been transported to this part of the myocardium, and hence identifying the regional perfusion defect.

**Perspective of model developments for clinical application**

The discrepancy between angiographic and physiology derived significance of a stenosis has been demonstrated in earlier studies (91). The major reason for this discrepancy relates to the complexity of describing all the details involved in calculating the flow and pressure field within and distal of a stenosis not captured by the Poiseuille and Bernoulli equations using simplified parameters of stenosis severity. More recently, there have been new attempts to apply computational fluid dynamics using meshes derived from images of stenotic vessels and from these to predict the significance of a stenosis by predicting FFR (51), although the future of this approach remains uncertain.

The field of evaluation of stenosis significance is rapidly evolving. The main developments can roughly be divided in those based on epicardial hemodynamic measurements and those on detection of regional ischemia. The perfusion measurement will find its place in preselection of patients prior to revascularization. However, within the cardiac catheterization laboratory, intracoronary hemodynamic measurements form the only resource for a physiological diagnosis of lesion severity on the spot.

Notwithstanding the significant improvement obtained with clinical outcome with the application of FFR compared to visual assessment using coronary angiography for clinical decision making (91), there is still much room for improvement. From a basic biophysical and physiological point of view, the model underlying FFR is oversimplified for a variety of reasons. FFR describes the hyperemic condition of the coronary circulation by linear resistances, thereby ignoring the fact that all vessels are distensible and hence vessel diameters change with pressure. Since resistance varies with diameter to the fourth power, this assumption of the FFR model is
most likely incorrect. The FFR model also ignores the effect of cardiac contraction on MR as has been discussed in recent reviews (90, 94). Moreover, it considers the resistance per unit mass for a healthy part of the myocardium the same as for that distal of a coronary stenosis, thereby ignoring remodeling of the microcirculation under the influence of the altered hemodynamic conditions (99). CFVR has the major disadvantage that it depends not only on hyperemic flow but also on baseline flow, which, in turn, depends on oxygen needs of the heart. However, conceptually, it is a good index since it expresses the real clinical and physiological issue of how much more flow can be realized distal of a stenosis by increased exercise. In a large percentage of patients, CFVR and FFR result in contradictory advice to treat, which was shown to be the result of variability in HMR (61, 63). Combined measurement of distal pressure and flow velocity allows the measurement of HSR, which is more specific for the lesion development since it is almost independent of distal events. It has been shown that this index performs better that FFR and CFVR (62).

The indices discussed above require in one way or another, the full vasodilatation of the vascular bed distal of a stenosis. The problem is the uncertainty about what maximal is. Increasing the dose of intracoronary adenosine injection tenfold results in a further decrease of FFR (23). The uncertainty about a well-defined maximal hyperemic state and the practical problems related to the application of adenosine has resulted in so called adenosine-free methods for establishing physiological stenosis severity such as iFR (79), BSR (93) or the pressure drop at given flow velocity at submaximal vasodilation (57).

Because of the complexity of the physiological processes and the many interactions between them, model developments as described in this paper are needed. This is also required to integrate measurements by different modalities such as MRI and epicardial hemodynamics (87, 101).

**Conclusions**

In this paper, we have reviewed major physiological and pathophysiological processes and their bearing on techniques for the diagnosis of coronary artery disease. The hemodynamic measurements distal of a stenosis provide the ability to quantify the overall results of a stenosis on coronary perfusion and the state of the coronary microcirculation. Moreover, it allows the study of the interaction between cardiac function and coronary flow dynamics. The developments in regional perfusion measurements are a major step forward in bringing physiology to the clinical arena since regional differences are induced by a stenosis. These regional differences are not only present between perfusion territories distal of obstructed and normal epicardial arteries but also within these territories, especially between subepicardial and subendocardial regions. Model developments allow the integration of all of these measurements at the epicardial level, from pressure and flow data, and regional information, provided by whole organ myocardial perfusion imaging. In addition to integrating data, the computational frameworks presented above enable the simulation of individual entities such as coronary occlusion or microvascular disease as well as analysis of physiological mechanisms such as the role that contraction or
ventricular pressure play on regional distribution of coronary flow. Our goal is that such models will provide a more complete picture of coronary physiology in normal and diseased cardiac conditions to enhance differentiation and personalization for diagnostic purposes as was the aim for the euHeart project.
References


