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Theoretical models for coronary vascular biomechanics: Progress & challenges

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Abstract

A key aim of the cardiac Physiome Project is to develop theoretical models to simulate the functional behaviour of the heart under physiological and pathophysiological conditions. Heart function is critically dependent on the delivery of an adequate blood supply to the myocardium via the coronary vasculature. Key to this critical function of the coronary vasculature is system dynamics that emerge via the interactions of the numerous constituent components at a range of spatial and temporal scales. Here, we focus on several components for which theoretical approaches can be applied, including vascular structure and mechanics, blood flow and mass transport, flow regulation, angiogenesis and vascular remodelling, and vascular cellular mechanics. For each component, we summarise the current state of the art in model development, and discuss areas requiring further research. We highlight the major challenges associated with integrating the component models to develop a computational tool that can ultimately be used to simulate the responses of the coronary vascular system to changing demands and to diseases and therapies.

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Keywords

Vascular structure; Mechanics; Haemodynamics; Mass transport; Regulation; Adaptation; Mathematical and computational model; Multi-scale; Cellular mechanics; Integration

1. Introduction

The aim of the cardiac Physiome Project is to develop theoretical models to simulate the functional behaviour of the heart under physiological and pathophysiological conditions. Heart disease continues to be the leading cause of morbidity and mortality in industrialised countries and throughout much of the world, and better methods for cardiovascular disease management are sorely needed (Ricotta et al., 2008). The overall clinical goal of *in silico* modelling is the development of patient-specific predictive models to improve diagnosis, therapy planning and treatment of cardiovascular diseases (Siebes and Ventikos, 2010). However, the achievement of this objective will also necessarily be underpinned by characterisation of the underlying physiological mechanisms derived from fundamental scientific investigation.

Using a multi-scale, multi-dimensional, and multi-disciplinary approach, theoretical modelling has the potential to predict clinical outcomes in order to achieve more effective healthcare. The aim is to develop individualised computer simulations that exploit patient-specific clinical visualisation modalities and experimentally obtained material properties in combination with solid mechanics and fluid dynamic models. Detailed knowledge about physiological (control) mechanisms and pathophysiological processes is necessary to arrive at clinically relevant decision-making tools. Ultimately, these models must account for processes operating at different time scales, ranging from transient behaviour of pressure and flow during a cardiac cycle, to effects of altered physiological demands or therapeutic interventions, through to much longer time-scale processes involving growth and remodelling due to disease progression and ageing (Lieber et al., 2005). New diagnostic methods evolving from this approach should allow better patient selection, targeted interventions, therapy assessment and predictions of therapeutic outcomes (Ricotta et al., 2008).

Heart function is critically dependent on the availability of an adequate blood supply to the myocardium. The network of coronary vessels must bring oxygenated blood within a small distance of every point in the tissue to meet the varying metabolic demands of the individual myocytes. In building mathematical models capable of simulating functional heart behaviour, it is therefore necessary to develop models for the coronary vasculature, in addition to models for sub-cellular function, cellular excitation–contraction coupling and cardiac tissue mechanics (see Clayton et al., 2011; Nordsletten et al., 2011). This article focuses on theoretical models for the coronary vascular system.

The ability of the coronary vasculature to meet the metabolic needs of heart tissue is facilitated by its dynamic structure, which is regulated on a short time scale via the active contraction and dilation of the small arteries and arterioles, and capable on a longer time scale of generating new vessels and remodelling existing vessels according to changing physiological and pathophysiological conditions. In addition to this wide range of temporal dynamics there are also many components of the coronary vasculature that interact over a range of spatial scales from sub-cellular to whole organ scale (see Fig. 1). To build mathematical models capable of simulating functional heart behaviour, we thus need to understand in detail the individual components of the coronary vascular system (including vascular structure and mechanics, fluid flow and mass transport, regulation and remodelling,

and cellular biomechanics) and how they work in an integrated way to respond to the ever-changing demands placed upon the coronary vascular system.

Embedding of current physiological understanding within mathematical frameworks is an approach that has already led to a number of important contributions for understanding coronary circulation over many years. We start by presenting a brief synopsis of the research that has provided the foundation for the current models. Within this historical summary the interested reader is referred to a number of recent and more comprehensive reviews. However, it is important to note that the large body of work in this area means that, rather than providing a thorough review, our goal in the sections which follow is to examine the current status of key theoretical models for each constituent component and their integration, and assess the modelling challenges that are currently defining the cardiac Physiome in the context of the coronary circulation.

Unique to the coronary circulation is the continuous and rhythmical compression of the blood vessels as the heart contracts, combined with the necessity to provide continuous perfusion to match a wide range of metabolic rates. This squeezing effect, or systolic flow impediment, was first proposed by Scaramucci in 1695 and has subsequently been investigated by Porter (1898), Anrep et al. (1927), Downey and Kirk (1975), Spaan et al. (1981), Bruinsma et al. (1988), Krams et al. (1989a,b), among others. In the models of Downey and Kirk (1975) and of Spaan et al. (1981) the compression effects of intramyocardial pressure were assumed to be equal to ventricular pressure at the endocardium and to decrease linearly to zero at the epicardium. Arts (1978) developed an integrated model of cardiac wall mechanics and the coronary circulation, in which the coronary microvessels were loaded by an intramyocardial pressure that was related to myofibre contraction through left ventricular pressure (Arts et al., 1979; Arts and Reneman, 1985). Later models also considered a direct interaction between the myocardium and the microvasculature, through stiffening of the myocardium during systole alone (Krams et al., 1989a, 1989b), or in combination with radial passive tissue stress (Beyar et al., 1993; Huyghe et al., 1992; Zinemanas et al., 1994; Vis et al., 1997; Bovendeerd et al., 2006). In particular, Krams et al. (1989a, 1989b) suggested a more limited role of ventricular pressure, and applied the “time varying elastance concept” of Suga et al. (1973) to explain systolic flow impediment. This concept emphasises the effect that time-varying ventricular wall stiffness, which is assumed to be independent of ventricular pressure, has on coronary blood volume. The theory of Krams et al. (1989a, 1989b) is based on the observation that flow impediment is similar for isovolumic (high systolic ventricular pressures) and low after load isobaric (low systolic ventricular pressures) contractions. However, the elastance concept does not explain why epicardial flows are not inhibited to the same degree as endocardial flows (Goto et al., 1991; Spaan, 1995) and subsequent studies again suggested that ventricular pressures have a significant effect on time-varying coronary flow.

Closely linked to this issue is the role of vascular resistance and compliance in determining coronary flow. The “vascular waterfall mechanism” proposed by Downey and Kirk (1975) sought to explain reduced coronary inflow by the increase in resistance resulting from the collapse of vessels embedded in the myocardium. However, since this throttling effect would impede both arterial inflow and venous outflow, this theory alone could not explain the increased venous outflow during systole. The introduction of the “intramyocardial pump model” (Spaan et al., 1981) accounted for the role of vascular compliance. In this model compliant vessels are filled from the high-pressure arterial side in diastole and then discharged through the low-pressure venous side in systole. This concept has since been extended in a number of lumped parameter mathematical models of coronary circulation, e.g. Bruinsma et al. (1988), to account for the variation in vascular resistance and

compliance throughout the coronary network with the temporal change associated with variation in intramyocardial pressure.

Key to understanding and unravelling the role of myocardial contraction on coronary blood flow has been the development and application of experimental measurement techniques to determine the temporal dynamics of myocardial blood flow across a range of vessel sizes. These experimental observations now include flows in the microcirculation (see reviews of Kajiya et al. (2008) and van den Akker et al. (2010)) and flows subject to varying mechanical conditions. These latter studies in particular have been instrumental in quantifying phasic variations throughout the cardiac cycle in both animal models (Kimura et al., 1992; Kajiya et al., 1989, 2005) and more recently humans in clinical contexts (see reviews of Spaan et al. (2006, 2008), Knaapen et al. (2009)).

In addition to capturing the dynamic interactions of flow and myocardial contraction, a further understanding of the control of coronary flow in both normal and pathological conditions is required; specifically the regulation of vessel resistance to match perfusion with the metabolic demands of the heart, in spite of fluctuating perfusion pressure. This tendency is termed autoregulation, and is the result of a large number of different physiological mechanisms (see reviews of Rubio and Berne (1975), Feigl (1983), Jones et al. (1995), Deussen et al. (2006), Duncker and Bache (2008), Zhang et al. (2008)).

A quick outline of some established concepts of autoregulation can be summarised as follows. In the heart, microcirculation plays a key role in regulation of flow since the majority (~70%) of the resistance, and the greatest capacity to adjust it, resides in the microvessels (Chilian et al., 1989). Previous studies have discovered many different mechanisms of regulation, including the major effectors of myogenic response, flow-induced dilation, metabolic control and conducted responses, as discussed in turn below.

The myogenic response is caused by contraction of vascular smooth muscle cells which respond directly to distending pressure in the lumen (Bayliss, 1902), with a typical time scale in the order of tens of seconds to minutes. Under normal flow conditions, the myogenic response provides the basal tone, producing the vasodilatory reserves which can be exploited by other regulatory mechanisms. Reduction in perfusion pressure has been observed to produce dilation predominantly in microvessels (Kanatsuka et al., 1989; Chilian and Layne, 1990), and graded responses were observed in vessels of different diameters, with the most sensitive myogenicity found in intermediate arterioles of diameter around 60 μ m in pig coronary vessels (Liao and Kuo, 1997).

Flow-mediated vascular dilation occurs when the vascular walls sense fluid shear stress, leading to local release of nitric oxide (NO) and relaxation of the smooth muscle cells. It has been shown that the presence of intact endothelium is necessary to initiate this process (Furchgott and Zawadzki, 1980; Pohl et al., 1986; Griffith et al., 1986). Although flow dependent dilation is readily observed in large coronary arteries (Hintze and Vatner, 1984) and venules (Kuo et al., 1993), studies in isolated vessels indicate that large arterioles exhibit the most sensitive response to flow stimuli (Kuo et al., 1995; Jones et al., 1995).

The metabolic control hypothesis proposes that coronary flow remains constant when subject to a fixed level of metabolic demand, as autoregulation is governed by a myocyte-produced substance which diffuses to the vascular smooth muscle cells via interstitium. Originally it was suggested that adenosine was the main substrate for metabolic control (Berne, 1963), but subsequent experimental results have failed to confirm this. There have been many other mediators proposed for the role, including bradykinin, CO₂ and H⁺, H₂O₂, potassium and endothelin. However, due to the redundant design of the metabolic control system in which blocking of any one of these substances fails to abolish the control

mechanism, it is now widely held that the metabolic control is achieved via a combination of many different mediators (Zhang et al., 2008).

The conducted responses in flow control and the oxygen sensing mechanism of the red blood cells have been the focus of some of the more recent modelling studies. In addition, it should be noted that coronary autoregulation is achieved via integrated interactions of the aforementioned mechanisms. The quantitative investigation of such a system is an ongoing challenge in the cardiac Physiome project, and is described in greater detail in Section 6.

A key step to characterising these autoregulator responses is a mechanistic understanding of endothelial function at the lower spatial scale of the cell. This in turn defines a central challenge of developing theoretical multi-scale models for the coronary circulation, that is, to understand the role of endothelial cells lining all blood vessels in vascular physiology and pathophysiology, and how they sense and modulate their function when exposed to changes in their local biochemical and biomechanical environment. The endothelial cell is particularly sensitive to fluid dynamical forces such as shear stress and pressure, in response to which they produce biochemical signals during the process of mechanotransduction (Dewey et al., 1981; Davies et al., 1984, 2005; Levesque and Nerem, 1985; Florian et al., 2003; Weinbaum et al., 2003; Mochizuki et al., 2003; Tarbell and Patakis, 2006). The surface of endothelial cells has two important specialisations that factor into mechanotransduction and solute transport: the glycocalyx composed of membrane bound highly charged macromolecules regularly distributed over the luminal surface (comprehensively reviewed by Reitsma et al. (2007) and Weinbaum et al. (2007)) and primary cilia – one per cell – that can project beyond the luminal surface as membrane bound continuations of the cytoskeleton (Kojimahara, 1990; van der Heiden et al., 2008). Both may play a role in endothelial mechanotransduction and the glycocalyx also acts as a transport barrier and as a porous hydrodynamic interface in the motion of red and white cells in microvessels (Weinbaum et al., 2003). These cellular elements are more extensively outlined in section 8.

This inherently integrative nature of coronary investigation combines experimental measurement and modelling. Such work is focused on understanding, arguably, one of the most complex vascular systems in terms of regulation, mechanical interaction and clinical pathologies. Below we aim to outline many of the research challenges faced in developing integrated mathematical models to describe the coronary vascular system which, if overcome, will also be invaluable in developing models to understand other organ systems.

As already highlighted, in order to build computational tools capable of simulating functional heart behaviour, we are faced with the challenge of integrating models for physical processes at disparate spatial scales, e.g. incorporating micro-scale flow and mass transport processes in a macro-scale model for myocardial tissue. The challenge is to introduce small-scale information into larger-scale models without the resulting models becoming computationally intractable. One approach is to use a lumped representation where fine-scale structures, e.g. blood vessels, smaller than a certain size are represented by a single compartment with uniform properties. A limitation of this simplified approach is that significant spatial variations may exist within this compartment, which are not represented by the model. An intermediate approach between detailed representation of fine-scale structure and a lumped approach is provided by homogenisation theory. In this theory, a local spatial averaging of fine-scale structure is achieved by exploiting asymptotic techniques to estimate macro-scale properties, based on explicit solutions in smaller-scale subunits (Huyghe et al., 1989a, 1989b; Vankan et al., 1997; Chapman et al., 2008; Shipley and Chapman, 2010; Shipley et al., submitted for publication). Although homogenisation techniques have been used for many years in modelling the mechanical properties of the

myocardium, the technique is now starting to be used more widely in cardiovascular fluid dynamics modelling, and we highlight this methodological approach in Section 9.

Because of the inherently multi-scale nature of the system we have chosen to present the research ideas by application (flow, mass transport, etc) rather than by modelling methodology, and stress that many of the same theoretical techniques are used in the development and solution of the component models. To model coronary flows, including the microcirculation and the large arteries and veins, we must understand the geometry of the flow domain, and the mechanical environment within which the vessels find themselves (determined both by the properties of the vascular wall and the surrounding myocardium). Such aspects are considered in Sections 2 and 3. We then consider flow and mass transport in Sections 4 and 5. Finally, we consider how coronary vasculature networks evolve on both short (regulation) and long (adaptation) time scales in Sections 6 and 7. The mechanisms by which endothelial cells sense fluid mechanical forces and produce biochemical signals in the process of mechanotransduction are considered in Section 8. Each section highlights the current state of the art of modelling in the field, before going on to explore open research challenges. In section 9 we discuss how the component models may be integrated.

2. Coronary vascular structure

2.1. Introduction

The human heart contains approximately 10^8 vessels that range over four orders of magnitude in calibre and length. The coronary microcirculation, consisting of vessels with dimensions less than about 200 μm (Popel and Johnson, 2005) contains more than 95% of the total coronary vasculature segments. These vessels are responsible for the major resistance to vascular flow, as well as short-term regulation (see Section 6) and long-term adaptations (see Section 7) that ensure the cardiac demands are satisfied at both local and global levels. However, despite years of research, a complete and concise description of the coronary microcirculation remains elusive – the vessel networks exhibit a heterogeneous and anisotropic 3D mesh-like organisation, with a vascular density that is some 5–10 times higher compared to other organs, which makes quantitative characterisation of its structure technically challenging. Similarly, the understanding of the structure of the small coronary arteries and veins commonly found to run intramurally, e.g. with regards to the extent of their collateralisation (Loukas et al., 2009c; Tayebjee et al., 2004), is incomplete.

In comparison, there are relatively complete descriptive characterisations of the large human coronary arterial network and its variations (Loukas et al., 2009a) and to a lesser extent, the venous system (Ho et al., 2004; Loukas et al., 2009b). At this level, the vessels largely follow a common branching pattern allowing assignments of standard anatomical ontologies and statistical ordering systems, and their quantitative and spatial distributions can be routinely obtained by clinical imaging modalities such as magnetic resonance imaging (MRI) or multi-detector computed tomography (MDCT) angiography.

When considering the coronary vascular network structure it is important to consider the spatial distribution of the segments embedded within the myocardium in addition to the network topology and morphology. The significant *cross-talk* between coronary flow and cyclical muscular contraction that is particular to the heart (Westerhof et al., 2006) gives rise to the unique pulsatility with out-of-phase pressure and flow waveforms and arterial/venous phasic differences in coronary flow. Thus it is not only the arterial-to-venous path travelled by an erythrocyte that matters, but also the dynamic interaction of blood with the intramyocardial stresses and deformations along the path which must be accounted for. This coupling effect is particularly pronounced in the microvascular compartment that forms the most extensive interface with extravascular structures.

Here we discuss the state-of-the-art techniques that are currently used to describe structure, including vascular casting and imaging, together with synthetic network generation techniques that can be used when such detailed structural information is not available.

2.2. Vascular casting

Vascular casting has been used since the 1970s for anatomical studies of vascular networks. Early studies investigated the coronary microvasculature using Microfil (Bassingthwaight et al., 1974) or catalysed polymer resin (Van Bavel and Spaan, 1992). Although this technique cannot be applied *in vivo*, it is still widely used for vascular anatomical studies because it preserves the complex geometry of the vascular network at high resolution, i.e. from full network structure to the individual cellular imprints on the endoluminal surface. More recent studies have combined radio-opaque Microfil with micro-computed tomography (μ CT, Jorgensen et al., 1998) or fluorescent dye suspensions in the resin (Spaan et al., 2005) to allow three-dimensional imaging, as outlined in Section 2.3. Such anatomical information acquired from the combination of casting with advanced imaging modalities is beneficial to integrative modelling, as it allows building of theoretical models of structure–function coupling based on multi-scale information.

A notable casting study was made in the early 1990s to obtain a comprehensive statistical characterisation of the coronary structure. In a series of publications, large networks of porcine coronary arteries (Kassab et al., 1993), veins (Kassab and Fung, 1994) and capillaries (Kassab et al., 1994) were examined manually to determine segment length and diameter, and to generate connectivity matrices. These studies yielded detailed morphological information on 11 orders of arteries and 12 orders of veins (divided into sinusal or thebesian types) using the Strahler classification system (Strahler, 1957), and highlighted the patent heterogeneity present in the coronary vasculature. A key motivation of this study was to reduce the vast amount of structural information into a form suitable for mathematical modelling, and its outcomes are an undeniably valuable contribution to this objective. This approach has been recently extended via non-invasive computed tomography (CT) imaging and computer-assisted analysis (Wischgoll et al., 2009). However, as discussed above, the approach of quantifying morphological variabilities strictly within artificially assigned orders may be misleading as it does not account for the coupling between structure and physiological function such as autoregulation and regional metabolic demand. The correlation between haemodynamic parameters and the vessel order is very scattered, and the assumptions underlying the ordering schemes may preclude such issues from being addressed. Moreover, due to the destructive technique employed in this study, information regarding the spatial distribution of segments cannot be recovered.

2.3. Structural imaging of coronary vasculature

During the past decade, vascular imaging technology and the associated automated analysis algorithms have rapidly improved. The best resolution data are still obtained using casting techniques, and effort has been directed at constructing custom devices to improve the resolution and coverage. Key examples include the large volume confocal imaging system (LVCIS) (Sands et al., 2005) and knife-edge scanning microscopy (KESM) (Mayerich et al., 2008). Both modalities operate on resin-embedded tissue by incrementally imaging a plane of tissue and mechanically removing slices to build up a three-dimensional dataset. They are capable of achieving 300–400 nm in resolution, and can thus fully resolve vessels of the microcirculation. However, these techniques are limited in the acquisition volume to a maximum of a few mm³ due to the requirement the samples are fixed in resin which must diffuse into the tissue. Confocal microscopy has been used for dual myocyte-vascular imaging which was used to understand their microstructural relationship (Lee et al., 2007). The imaging cryomicrotome device (Spaan et al., 2005) was purpose-built to image larger

samples and can image the coronary network of a whole human sized heart with less than 25 μm voxel dimensions. This device also allows the coronary flow distribution across the myocardial wall to be quantified based on detection of fluorescently labelled microspheres that are injected under different conditions *in vivo* (van Horssen et al., 2009, 2010).

Specialisations of more conventional modalities, such as CT or MRI, have also been used to achieve high-resolution vascular imaging. This was demonstrated in the hierarchical CT/ μCT /synchrotron radiation μCT (ST μCT) imaging study (Heinzer et al., 2006) and 11.7T MRI study (Burton et al., 2006). These devices are subject to cost and availability issues, but present a promising avenue for future investigations. The scope for automatic segmentation of coronary μCT images has been demonstrated recently (Lee et al., 2007) (see Fig. 2a). At the translational end of the research spectrum, non-invasive clinical CT (Kumamaru et al., 2010) or MR (Friedrich, 2010) modalities are now used routinely for *in vivo* imaging of patient-specific large vessel geometries, and some have been combined with 3D flow modelling (e.g. De Santis et al., 2010). Although these applications are generally limited by resolution and field of view, they offer a number of possible approaches to *in vivo* dynamic imaging of vasculature. Clinically, epicardial vessel geometries can be extracted using CT or MR and then mapped onto MR derived dynamic deformation changes (Torii et al., 2009). Such fusion of multimodality images offers scope for overcoming specific limitations of each imaging device, and thus hybrid imaging has become a topic of much interest in cardiovascular imaging research (Slomka et al., 2008).

2.4. Synthetic network generation

Prior to the advent of high-resolution 3D imaging, attempts have been made to obtain detailed coronary geometry by computationally generating synthetic networks in a stochastic manner. The algorithms employed combined a data-driven approach, for which the detailed cast dataset described above was used extensively, with a mechanism-driven approach, which sought to utilise theoretical optimality principles discussed below. Examples range from networks which achieved full arterial reconstructions matching the observed statistical distributions (Kassab et al., 1997; Mitta et al., 2005) to networks satisfying given pressure drops and flow rates, that also assigned spatial locations to segments (Schreiner and Buxbaum, 1993). Others combined these approaches by stochastically generating segments informed by a known morphological distribution that were then arranged into a given 3D volume through self-avoidance functions (Beard and Bassingthwaite, 2000a, 2000b; Smith et al., 2000) (see Fig. 2b). The most recent study in this direction extended the application to a full ventricular geometry (Kaimovitz et al., 2005).

Although the generated networks exhibit plausible realism and many serve as surrogates for native networks in haemodynamic analyses, many questions remain to be addressed. The main question concerns the crudity of the metrics used to confirm the validity of the network – the determinants of coronary flow are still an open question, and the origins of the substantial heterogeneity are poorly understood. In particular, the current morphological data do not relate in any way to the local conditions of the tissue metabolic demand or the mechanical conditions, which are known to be highly heterogeneous (Decking, 2002).

The lack of complete anatomical information can erroneously grant plausibility to generated models, and this has been echoed by Beard and Bassingthwaite (2000a, 2000b) who remarked that their construction of a capillary network based on very simple rules was able to reproduce the then-available anatomical observations. Moreover, since the anatomical parameters are given as statistical distributions, valid conclusions may be drawn from a study that employs the synthetic networks only if it is repeated over many different stochastic realisations. This may have serious implications on its practicality. In addition,

haemodynamic studies performed on generated networks have a fundamentally limited scope for experimental validation.

2.5. Optimality principles

Speculated design principles underlying the vascular structure were first analysed quantitatively when Murray applied theoretical modelling in his seminal paper, which opened with ‘Physiological organization, like gravitation, is a “stubborn fact”’ (Murray, 1926). Murray’s optimality principle assumed that each vessel diameter minimizes a cost consisting of the sum of the viscous dissipation in the vessel and a term proportional to vessel volume. According to this theory, flow is proportional to the cube of vessel diameter and wall shear stress is the same in all vessels (neglecting effects of viscosity variations). This optimum state could in principle be achieved by adjustments of vascular diameter in response to deviations of shear stress from a set point (Rodbard, 1975; Sherman et al., 1989). However, vessels respond to many stimuli besides wall shear stress, e.g. pressure (Bakker et al., 2003) and oxygen concentration (Hacking et al., 1996). Since its introduction, many subsequent models have considered additional mechanisms with increasing biophysical detail, incorporating the effects of non-Newtonian rheology (Frame and Sarelius, 1995; Matsumoto et al., 2004; Kiyooka et al., 2005; Revellin et al., 2009), vascular metabolism (Liu and Kassab, 2007; Taber, 1998), pulsatile flow (Painter et al., 2006) (relevant for the coronary circulation), and arterial branching (Zamir, 1976).

In reality the vascular system shows large deviations from Murray’s law: e.g. it has been shown that in the microcirculation shear stress varies with local pressure (Pries et al., 1995). While optimality principles can be helpful in understanding the overall structure of vascular networks, they have significant limitations. Firstly, minimizing an energy cost does not necessarily take into account the functional requirements and constraints that apply to the system. No study has yet incorporated the metabolic requirements and perfusion volume of the surrounding tissue into Murray’s optimality framework. Secondly, the energy minimum can be broad, allowing large variations in structure. It is instructive to note that in the original Murray’s law, the “cube law” exponent may be varied from 1.5 to 10 with only a 5% difference in the energy cost (Sherman et al., 1989), and the significant scatter observed in the anatomic branching angles correspond to only a 2% deviation from the optimality of minimum drag hypothesis (Zamir and Bigelow, 1984). Thirdly, there is no a priori reason to assume that evolutionary processes have achieved a true optimum.

It is clear that considerable further effort will be required to elucidate vascular design principles, whether a stubborn fact or not. In light of the known stimuli that lead to structural adaptations (discussed in Section 7.7), incorporating such details may help to account for some of the physiological deviations from Murray’s optimum. In addition, it may be necessary to account for the different mechanical conditions to which the vessels are exposed, within different regions of the heart (see Section 3). However, there is no inherent mechanism for sensing optimality, except long-term evolutionary advantage, and, more recently, alternative theories for structural adaptation have developed, which have focused on identifying the signals and stimuli that are available to individual components of the vascular system in order to understand how responses to such signals can lead to observed vascular system behaviours and structures. This is discussed further in Section 7.7.

2.6. Challenges

The rapid recent progresses in coronary vascular structural characterisation highlights a number of major challenges for future research efforts. To aid modelling studies of coronary haemodynamics and associated adaptation/mass transport processes, a concise description of the vascular structure is required. Such a description will ideally capture the key

determinants of flow with few parameters to aid model reduction and be physiologically meaningful to aid model interpretation. This information should be derived from detailed studies of coronary vascular structures, which are now possible to obtain. Also, recognising that the vasculature is a dynamically adapting system in response to short and long-term stimuli (see Sections 6 and 7), structural studies spanning different stages of pathology will contribute to our fundamental understanding of the vascular structure–function and the etiology of the diseases. In addition, these studies should address both the topological complexities and the spatial organisation of the vascular network, if the coupled coronary flow–cardiac contraction effects are to be understood.

3. Mechanical properties

3.1. Introduction

Knowledge of the mechanical properties of the coronary vasculature and its surrounding myocardial tissues is essential for the modelling of flow in the coronary system and its relation to cardiac muscle contraction (Zhang et al., 2004). The main characteristics of coronary flow can be analysed using pulse-wave velocity network models (e.g. Reymond et al., 2009; Alastruey et al., 2009b; Bessems et al., 2007). These network models form the boundary conditions for local 3D flow phenomena in the large coronary arteries (Quarteroni and Formaggia, 2004), and are the basis for inflow conditions for models of the myocardial microcirculation (Matsumoto and Kajiyama, 2005). In the following sections, we highlight the importance of knowledge about the mechanical properties of the different structures in the cardiac tissue and vasculature and indicate how these properties can be obtained experimentally enabling their use in models of coronary flow, myocardial perfusion and contraction.

3.2. Mechanical properties of smaller vessels – the role of the myocardium

The mechanical properties of the small arteries, the arterioles and the microcirculation, which are all embedded in the surrounding myocardial tissue, are difficult to determine. However, due to the limited wall thickness of these vessels, the wall motion of these small vessels is dominated by the time-dependent dynamics of the surrounding tissue environment (Goto et al., 1996; Sorop et al., 2003). During systole, the effect of cardiac contraction on perfusion is manifested as a decrease of coronary arterial inflow and an increase of coronary venous outflow. In turn, coronary pressure affects cardiac muscle contraction and oxygen consumption (Gregg, 1963; Dankelman et al., 1999) and coronary filling affects muscle stiffness and perfusion. This two-way interaction between the cardiac muscle and perfusion is called mechanical cross-talk (Westerhof et al., 2006). While fundamental to coronary dynamics, characterisation of these interactions remains a complex challenge as evidenced by several studies that have demonstrated that during normal contraction, intramural vessels are shielded from the high systolic left ventricular pressure by the myocardium itself (Kouwenhoven et al., 1992; VanTeeffelen et al., 1998). The strong interplay between cardiac contraction and vascular flow has been shown to depend on the transmural location of the vessel in the heart wall, and similar types of arteries in different myocardial positions have different wall thickness (Choy and Kassab, 2009).

Several models have been proposed to explain aspects of mechanical cross-talk. Some explain basic interaction mechanisms for a representative discretely modelled blood vessel (Downey and Kirk, 1975; Arts, 1978; Arts et al., 1979; Arts and Reneman, 1985; Spaan et al., 1981; Bruinsma et al., 1988; Krams et al., 1989a, 1989b; Beyar et al., 1993; Huyghe et al., 1992; Zinemanas et al., 1994; Vis et al., 1997; Smith, 2004; Bovendeerd et al., 2006). Although extensions to several thousands of vessel segments have been presented (Lee et al., 2009) it seems unlikely that flow in the complete coronary vascular tree can be modelled

through a discrete approach. An alternative approach which still retains local spatial variations is to use homogenisation theory, in which averaging of the fine-scale structure is achieved by exploiting asymptotic techniques to model tissue-scale properties. This approach is used in the model proposed by Huyghe et al. (1992), which represents the myocardium as a two-phase mixture. The solid phase represents the myocardium. The fluid phase is composed of several compartments, representing the blood in the hierarchical structure of the coronary tree. The model employs a 4D space, consisting of the traditional 3D space augmented by a fourth dimension that describes the organisation of the vascular bed from arteries through arterioles, microvessels and venules to veins. 4D blood flow and pressure gradients are coupled through a 4D permeability tensor. The latter tensor is derived from the anatomy of the vascular bed through a formal averaging procedure (Huyghe et al., 1989a, 1989b; Vankan et al., 1997). Homogenisation approaches may be validated by comparison of the results with simulations with many vessels represented as discrete structures to account for microvascular flows in cardiac tissue. The potential for homogenisation approaches to be used in other aspects of coronary vascular system modelling is discussed in more detail in section 9.

In both discrete and continuum models of the coronary circulation, models for the mechanical properties of the passive and active myocardium are needed. To represent these constitutive properties a homogenisation approach is also often applied. Commonly, the passive myocardium is considered virtually incompressible, anisotropic and non-linearly elastic. This behaviour is described phenomenologically through a strain energy density function, with a volumetric part to control tissue volume change and an additional part to describe the response to deformation. Common choices for the latter part are an exponential function or a pole zero law with stress growing unboundedly in terms of normal and shear strain components with respect to a local material-bound coordinate system (for further details see Nordsletten et al. (2011)).

Early approaches to describe the active myocardium used phenomenological, tissue-level models. These few-parameter models enable systematic evaluation of the force-time, force-length and force-velocity relations on cardiac mechanics and coronary perfusion. Obviously, they lack the coupling to (pathologies at) the cellular level, that is present in more recent models in which the complete sequence of events from depolarisation of the cell membrane, through to cross bridge formation and subsequent force generation, is described. Pitfalls and challenges encountered in using such latter models, related to combining detailed sub-models into an overall model, have recently been reviewed by Lee et al. (2009).

3.3. Mechanical properties of large coronary arteries

The flexibility and active properties of the large arteries strongly influence the flow patterns within them. Simulation of blood flow requires knowledge the mechanical properties of the arterial wall. For fluidstructure interaction (FSI) simulations, full 3D constitutive relations between tissue stress and strain tensors are required. Examples are models from the Holzapfel/Humphrey family (Holzapfel et al., 2000; Humphrey, 2001). This family includes fibre-reinforced models for the arterial wall which incorporate the microstructural features of collagen fibres and morphological information about the different layers. Simpler phenomenological models include exponential, Truesdell-like, power law models for neo-Hookean material (Truesdell and Noll, 1965; Raghavan and Vorp, 2000). The advantage of the more complex, fibre-reinforced models is that the role of smooth muscle cells can be accounted for within the theoretical framework (Zulliger et al., 2004). The main disadvantage of these complex models is that they contain large numbers of parameters that are difficult to determine in a simple experiment. One approach to overcome this difficulty is to exploit reverse engineering techniques by using a hybrid experimental-numerical

approach (Oomens et al., 1993). The main issues in obtaining these parameters are related to pre-straining and the role of residual stresses (Zulliger et al., 2004).

3.4. Mechanical properties for the coronary venous system

In contrast to the situation in the systemic circulation, the coronary venous system cannot be viewed as a reservoir of blood at a relatively low-pressure collecting blood from the microcirculation, with a quasi-static resistance to flow that is small compared to the resistance of the microcirculation. The coronary veins are periodically squeezed by the heart muscle contraction resulting in a flow with a significant pulsatility and a time-varying non-linear resistance and compliance. Constitutive relations between tissue stress and strain tensors of the veins and inclusion of the forces that originate from myocardial contraction are required to model these phenomena.

3.5. Mechanical properties for coronary pulse-wave models

When considering networks of large vessels, pressure and flow distributions can be modelled as travelling pulse waves along the vascular network (see Section 4.4). Pulse-wave velocity and attenuation are determined by geometrical properties, e.g. wall thickness and lumen diameter, and mechanical properties, e.g. anisotropic elastic or visco-elastic properties of the arterial wall, the non-Newtonian viscous properties of blood and, indirectly, by the mechanical properties of the surrounding tissue. Consequently, lumped parameter models (0D) and wave propagation models (1D) (see section 4.4 below) that describe pressure (p), cross-sectional area (A), and flow (q) or velocity ($v = q/A$) relations in the coronary network require the linear or non-linear properties of the arterial wall to be defined. In the simplest case, a model for arterial compliance in which the pressure depends on the arterial cross-sectional can be used and data can be obtained by invasive or non-invasive *in vivo* or *ex vivo* determined pressure–area relations. This relation can then be used to eliminate one of the three independent variables from the set (p, q, A) leading to either a (p, A)- or a (p, q)-formulation. However, when either non-linear or visco-elastic constitutive relations are employed (see Reymond et al. (2009) for an overview), this elimination is not straight forward and a (p, q, A)-formulation is used (Bessems et al., 2008). The same formulation can be used if instead of a pressure–area relation an axisymmetric model of a thin or thick walled tube is used to close the system of equations (e.g. Huberts et al., 2009). Such a model requires material geometrical properties, e.g. wall thickness, wall composition and composition dependent shear and bulk modulus. More complicated models based on fibre-reinforced material behaviour (Holzapfel et al., 2000) are currently not applied in 1D wave propagation models although in theory this extension is possible once the model parameters are known. As mentioned earlier pre-strain and residual stress are complicating factors. Consideration must also be given to flow characteristics at arterial sites of local geometric complexity such as branches and bifurcations of the coronary arteries. The pulse waveforms and flow separations are extraordinarily difficult to estimate and undoubtedly are responsible for the biological susceptibility to atherosclerosis at such locations (e.g. see Wischgoll et al., 2009).

As the coronary arteries, for a large part, are embedded in the cardiac muscle, the passive and active mechanical properties of the myocardium (see Section 3.2) are key to determining the mechanical coupling to coronary flow (Guiot et al., 1990). For the large coronary vessels, the motion and deformation of the myocardium can be considered to be a boundary condition on the flow domain. For the coronary pulse-wave equations, the outflow microcirculation can be incorporated in the outflow boundary condition, and in general a pressure–flow relation is specified. This relation can follow from a simple windkessel model. Alternatively, more advanced models (described earlier in Section 3.2) can be employed that incorporate the intramyocardial pressure and its influence on compliance and

resistance (see Zinemanas et al., 1994; Bovendeerd et al., 2006). Furthermore, by modelling the microcirculation as a network of vessels, aspects of growth and remodelling can be incorporated and explored.

3.6. Challenges

A challenge in the development of the continuum approach to model large numbers of vessel segments is to exploit detailed information on the anatomy of the vascular bed. A further consideration is to incorporate effects of vascular adaptation by active regulation of vascular smooth muscle tone and via remodelling within the continuum approach. Additionally, the development of poroelastic continuum models (Ng et al., 2005; May-Newman and McCulloch, 1998; Huyghe et al., 1992) will not only provide local and time-dependent pressure–flow relations, but also has the potential to describe the influence of perfusion on passive/active properties of the myocardium. Attention should also be given to methods of coupling continuum models for networks of microvessels to discrete models for large arteries.

From a disease standpoint, it is important to consider the effect of cardiac contraction on the transmural distribution of blood flow and the vulnerability of the subendocardium, especially in the presence of an epicardial stenosis (Bache and Schwartz, 1982; Hoffman and Spaan, 1990; Austin et al., 1994). From a physiological point of view, the relative duration of diastole as a function of heart rate is an additional important parameter of subendocardial perfusion (Merkus et al., 1999, 2001; Fokkema et al., 2005; van den Wijngaard et al., 2008). Ultimately, such models should endeavour to include effects of endogenous regulatory mechanisms and pharmacological responses of the coronary microcirculation that are active *in vivo* (Hoffman and Spaan, 1990; Komaru et al., 2000).

Most importantly, the models should be tested by comparison with experimental data. Initial experiments could involve small tissue samples, e.g. trabeculae and papillary muscle. Compared to the *in situ* heart, small samples allow for easier control of experimental conditions and easier access for measurements. Such experiments can be used to test both discrete network and continuum models. In the future, isolated (Langendorf or beating) heart experiments would offer a testing platform (see e.g. de Weger et al., 2010). Similarly, advanced measurements to determine the mechanical properties of coronary arteries and veins by applying physiological loads in a physiological environment (see e.g. van den Broek et al., in press) should be carried out.

4. Blood flow

4.1. Introduction

Healthy human blood is a concentrated suspension containing red blood cells (RBCs) at a concentration (haematocrit) of 40–45%. Unstressed human RBCs are biconcave discs with a diameter of about 8 μm . In vessels with diameters much larger than this, blood can be considered as a continuum with a viscosity that is approximately constant at normal physiological shear rates. However, the finite size of RBCs results in non-continuum behaviour in narrow vessels. This gives rise to several effects which should be considered when simulating flow in the microcirculation.

The flow characteristics exhibited in the coronary vascular tree vary markedly from the microcirculation, to flow in the large coronary arteries. The Reynolds number for blood flow in the microcirculation is very small, typically in the range 0.001 to less than 1, and the flow is laminar and governed by the Stokes equations. In many tissues, flow pulsatility is strongly damped by viscous effects in combination with vascular compliance before it reaches the microvessels. However, in the myocardium, the contraction of the surrounding tissue may

result in a significant pulsatile component (see Section 3.2). In this case, the flow may be analysed using a quasi-steady approximation.

In contrast, the Reynolds number for flow in the large arterial vessels is high, typically in the range of hundreds, and this provides particular challenges in flow modelling. The well-known sensitivity of high-Reynolds number flows to geometric features is complicated by the dynamic nature of the flow domain, where vessels undergo continuous changes in shape and orientation, generating unusual kinematic and inertial contributions to the governing dynamics (Lynch et al., 1996). Flows are additionally subject to time-dependent upstream and downstream boundary conditions associated with cardiac pumping and distal vessel compression (as outlined in Section 3.5).

One-dimensional (1D) ‘reduced’ pulse-wave modelling provides a good compromise between computational cost and accuracy when a global assessment of blood flow in the cardiovascular system is required. This approach can be used to simulate the changes in blood pressure and flow in time and along the axial direction of large (coronary and non-coronary) vessels produced by the contraction of the heart. These changes propagate in the form of waves, called pulse waves, which carry valuable information about the morphology and functionality of the cardiovascular system.

In the following sections, we consider in detail microcirculatory flows, 3D flow modelling in large vessels, and reduced 1D pulse-wave models. For ease of presentation, relevant research challenges are highlighted at the end of each section.

4.2. Blood flow in the microcirculation

When blood flows in narrow tubes, the concentration of RBCs within the tube (tube haematocrit) is less than the RBC concentration in the blood entering and leaving the tube (discharge haematocrit). This Fåhræus effect (Fåhræus, 1928) arises from the fact that RBCs travel faster than plasma on average and therefore have shorter transit times.

Resistance to blood flow in narrow tubes is conveniently expressed in terms of the apparent viscosity, defined as the viscosity which, when substituted in Poiseuille's law, would give the same flow rate for a given tube length, diameter and pressure drop. In glass tubes the apparent viscosity declines substantially with tube diameter at diameters below 300 μm , a phenomenon known as the Fåhræus–Lindqvist effect (Fåhræus and Lindqvist, 1931; Martini et al., 1930; Pries et al., 1992). At diameters near the minimum which allows passage of RBCs (about 3 μm) this effect is reversed. An empirical equation (Pries et al., 1992) describes the variation of apparent viscosity with tube diameter and discharge haematocrit. The reduction in apparent viscosity in narrow tubes results mainly from the presence of a layer of cell-free or cell-depleted plasma near the tube wall. A good fit to experimental results for diameters 30 μm and above is obtained by assuming a two-phase model of blood flow, in which a central cylindrical region with viscosity three times plasma viscosity is surrounded by a plasma layer with a fixed width of 1.8 μm (Secomb, 1995). It should be noted that this width is a fitted parameter and has not been predicted from the mechanical properties of RBCs.

Experimental observations of distributions of flow and haematocrit in microvascular networks indicate that flow resistance in living microvessels is substantially higher than in glass tubes with corresponding diameters (Pries et al., 1990). An empirical formula for the viscosity of blood *in vivo* has been developed (Pries et al., 1994), based on data obtained in the rat mesentery. The principal cause of the difference between *in vitro* and *in vivo* blood viscosity in microvessels is believed to be the presence of the relatively thick endothelial surface layer (ESL, also called glycocalyx) bound to the inner surface of endothelial cells,

that may be up to 1 μm in width (Pries et al., 2000). The presence of this ESL leads to the exclusion of red blood cells from the region near the vessel wall and a consequent reduction in the tube haematocrit, defined as the fraction of the tube volume occupied by red blood cells (Constantinescu et al., 2001; Klitzman and Duling, 1979). Studies in which the ESL was experimentally manipulated (Vink and Duling, 1996) yielded information about the biophysical properties of the layer, which provided a basis for theoretical analyses of the mechanical interactions between the layer and flowing blood (Damiano et al., 1996; Han et al., 2006; Secomb et al., 2001).

At diverging microvascular bifurcations, the partition of RBCs into the downstream branches does not generally correspond to the partition of total blood flow, with the result that different haematocrits are found in the downstream branches. Generally, the higher-flow branch receives a higher haematocrit. Based on observations in the rat mesentery, empirical relationships have been developed to describe the dependence of phase separation on the vessel diameters and on the haematocrit of the parent vessel (Pries et al., 1989). A more recent version gives consistent behaviour under a wider range of conditions (Pries and Secomb, 2005).

The relationships described above provide a basis for predicting the steady distributions of velocity, flow rate, wall shear stress, pressure and haematocrit in microvascular networks with known topology and geometry subject to suitable boundary conditions. For this analysis, the network can be considered as a set of interconnected resistances. At each node in the network, conservation of flow leads to a linear equation in the pressures at that node and the adjacent nodes. This system can be solved efficiently for large networks using successive over-relaxation (Pries et al., 1990). If the non-uniform partitioning of haematocrit at bifurcations is included, a further iterative procedure is required in which haematocrits are updated based on current flows and the updated values are used to recompute flow resistance in each segment. Computation of unsteady haematocrit distributions in microvascular networks is more demanding, requiring the solution of coupled systems of hyperbolic PDEs (Pop et al., 2007).

As described above, empirical equations provide an adequate basis for simulating blood flow in microvascular networks. However, some limitations should be noted. The equations are based mainly on experimental observations of blood flow in the mesentery, a tissue which provides exceptionally clear visibility of microvascular networks. Corresponding data for the heart are not currently available. While the flow behaviour of RBCs is presumably independent of tissue type, the ESL has not been studied in the myocardial microcirculation. In principle, the rheological behaviour of blood in microvessels should be predictable, but this will require better understanding of the intrinsic mechanical properties of RBCs and their interaction with the plasma and each other at the haematocrits typical of microvessels. For single-file flow in capillary-sized tubes, this has been achieved (Secomb, 1987). However, the computational analysis of multiple interacting RBCs remains a topic of current research (Zhang et al., 2009).

The approach outlined above requires an explicit description of network geometry and topology including the smallest vessels. As discussed in Section 2.1, gathering such information is challenging, not least since a complete description of the heterogeneous and anisotropic coronary microcirculation is still outstanding. Techniques to predict relevant flow and mass transport parameters based on statistical properties of network structure could be valuable in such cases. Homogenisation theory can be used to estimate tissue-scale flow and transport properties, based on explicit solutions for flow and transport in smaller-scale subunits (Shipley and Chapman, 2010). When applied to the microcirculation, this approach faces difficult challenges because structural and functional parameters in the

microcirculation show large heterogeneity on a wide range of spatial scales (see Section 9.1).

4.2.1. Challenges—Several other aspects of microvascular flow should receive future attention. As already mentioned, unsteady effects may be relevant in myocardial microcirculation (Westerhof et al., 2006). Further analysis of unsteady flow in coronary arterioles is needed to clarify the boundary conditions on simulations of coronary arterial flow. The major function of the microcirculation is mass transport, and flow models must be linked to transport models. Regulation of blood flow occurs mainly in the microcirculation, and both flow regulation and changes in vascular structure have fundamental effects on cardiac function (see Section 6 and 7 for a detailed discussion).

4.3. 3D flow modelling in larger vessels

Despite the challenges presented when studying high-Reynolds number flows in large coronary arteries, it is important to be able to explore the influence of detailed 3D flow features on the biological response of the arterial wall, mediated for example by shear stress transduction or uptake at the arterial wall of transported species such as low-density lipoproteins (LDL), because of the focal nature of coronary artery disease, and even the athero-susceptibility of disease in the physiological state (see Section 8.2). It is necessary to be able to couple large-scale flow and luminal transport simulations with more detailed models of flow and transport properties close to the arterial wall, accounting for example for the local topography of the endothelium (Van Doormaal et al., 2009) (shown to lead to heterogeneous mass transfer over an individual cell) and the detailed structure of the endothelial glycocalyx layer (Vincent et al., 2008) (where the fluctuating particulate nature of blood will be apparent and through which adhesive interactions between blood-borne cells and endothelium may take place). It is also important to integrate flow models with detailed biophysical models for transport and mixing of species such as NO (Tsoukias, 2008).

The ability to simulate flow and the associated stresses in larger vessels with anatomically accurate geometry has seen a significant advance over the past decade. This technology has been aided by the availability of medical imaging techniques, e.g. MRI and CT, and suitable computational flow modelling tools originally developed for other disciplines such as the aeronautical industry. The simulation tools and computational resources now exist to simulate pulsatile, Newtonian flow in coronary arteries under a rigid wall assumption provided vessel anatomy and appropriate boundary conditions are available. However obtaining vessel anatomy and boundary conditions is a challenging task both from an imaging and modelling perspective (Steinman, 2002). Non-Newtonian models are also available: however, while methods for incorporating non-Newtonian models into large vessel simulations in the systemic circulation are well developed (Leuprecht and Perktold, 2001), the challenge is to determine and develop the appropriate non-Newtonian models for complex flow environments. It is also possible to introduce prescribed wall motion into flow simulations if this motion is known a priori (see Section 2.3 for details of current dynamic imaging methods). Alternatively the technology exists to model fluid–structure interaction within large vessels where the blood flow and wall motion are dynamically coupled. This type of modelling, however, is significantly more challenging and a key limitation to such an approach is our currently poor understanding of how the vessel is constrained by the adventitia and surrounding tissues. Furthermore, such an approach requires an accurate definition of the vessel wall geometry and the wall structural properties.

It is often argued that vessel geometry and flow pulsatility are the primary determinants of the flow features and their associated temporal and spatial stresses within large vessels. The

cyclic curvature deformations of coronary vessels have a strong effect on the distribution of shear stress (Lynch et al., 1996; Waters and Pedley, 1999; Van Meerveld and Waters, 2001; Moore et al., 2001; Weydahl and Moore, 2001). Effects such as non-Newtonian properties and the luminal displacement in coronary arteries are believed to have a secondary affect on the flow structure typically changing the magnitude rather than the character of the flow. The key determinants of accurate flow modelling therefore lie in the ability to obtain and reconstruct accurate anatomic data and boundary conditions. Whilst the development of imaging protocols are being advanced (see, for example, Section 2.3), the ability to reconstruct this data has been actively researched and there now exist both commercial tools, such as Amira, and open access software such as the imaging tool kit (ITK) (<http://www.itk.org>) and vascular modelling tool kit (VMTK) (<http://www.vmtk.org>).

As well as providing insight into flows under physiological and pathological conditions, 3D flow modelling is essential to understand the nature of flows that arise as a result of clinical intervention, e.g. coronary catheterisation which uses catheters to treat complications like angina, atherosclerosis and heart attack (Ganz et al., 1985; Doucette et al., 1992; Di Mario et al., 1995). To accurately assess the influence of catheters on *in vivo* flow conditions, it is essential to understand arterial flow and pressure variation along vessels when a catheter is present (Back et al., 1996; Bjorno and Pattersson, 1976a, 1976b). Analytical models, coupled with *in vitro* experimental evidence, have been developed to estimate the mean resistance increase due to the presence of the catheter (Back, 1994; Back et al., 1996). These studies have been extended to account for more realistic features such as artery curvature, degree of vessel stenosis, flow pulsatility and catheter flexibility (Jayaraman and Dash, 2001; Dash et al., 1996, 1999; Jayaraman and Tiwari, 1995; Sarkar and Jayaraman, 1998, 2001). For translating the models as tools for clinical use, modifications need to be included that consider the length, shape and size of the stenosis, catheter size and positioning, coronary artery wall properties, etc. Inclusion of all these complexities requires the use of 3D models and computational fluid dynamics.

3D flow modelling can also be used to further our development and understanding of techniques for clinical measurements. For example, highly flexible sensor-equipped guide wires with a diameter of only 0.3 mm are now used relatively routinely to measure velocity and/or pressure dynamics in the larger coronary vessels (Siebes et al., 2004). The effect of these wires on coronary flow or pressure is small, especially when the eccentric location of the guide wire within the vessel is taken into account (Sinha Roy et al., 2006; Verberne et al., 2007; Banerjee et al., 2008). At a research level, it is also possible to obtain dynamic velocity profiles in small epi- and endocardial vessels (Chilian and Marcus, 1982; Toyota et al., 2005).

4.3.1. Challenges—The large amount of numerical data generated from three-dimensional unsteady flow simulations must be processed at different levels of detail for different audiences. Maps of quantities of biological significance (such as wall shear stress distributions or wall uptake of a transported species) may be of interest to a clinical audience, while other quantities (for example cross-sectionally integrated pressure and flow distributions) must be considered if a 3D model of a stenosis or bifurcation is to be integrated with a 1D model of an arterial network (see Section 4.4). It is likely that a variety of other quantities – yet to be identified – will need to be interrogated as new biological mechanisms are identified and new generations of mathematical models are developed to understand them. The ability to generate 3D data also enables the research community to interact with asymptotic models of flow in deformed vessels where (if the underlying assumptions of these models are corroborated) a better understanding of the important dynamics of the problem will ensue (Waters and Pedley, 1999).

For clinical applications, these models ultimately should incorporate the altered material properties, haemodynamic environment and pathophysiological conditions associated with various disease processes of the coronary arterial wall, as well as microvascular dysfunction, valvular disease and cardiomyopathies that affect coronary–cardiac interaction (Garcia et al., 2009; Heusch et al., 2009; Weinberg et al., in press). This will require an integrated concerted effort of basic and clinical scientists from various disciplines in order to provide experimental evidence to support model development or corroborate the predictions.

Such models could then be used to optimize treatment that is tailored to a specific patient, pinpoint stenoses that require intervention, predict outcomes of minimally invasive surgical interventions or optimize application of intravascular and ventricular assist devices (Moore et al., in press; Rummelink et al., 2007; Kolyva et al., 2010; Ponzini et al., 2008; Voigt et al., 2009).

4.4. 1D pulse-wave modelling

As discussed in Section 3.5, in the large arteries pressure and flow distributions can be considered as summations of travelling pulse waves along the vascular network. As the pulse wavelengths are (at least) three orders of magnitude larger than arterial diameters in normal conditions, it is reasonable to use the so-called long wave approximation. This approximation leads to the 1D governing equations for an incompressible fluid filling a compliant vessel after integration of the incompressible Navier–Stokes equations over a generic cross section of a cylindrical domain (Canic and Kim, 2003; Quarteroni and Formaggia, 2004; Smith et al., 2002). The 1D equations also follow from direct application of conservation of mass and momentum to a compliant 1D control volume of incompressible fluid (Peiró and Veneziani, 2009; Sherwin et al., 2003). The 1D formulation has been satisfactorily tested by comparison against *in vivo* (Olufsen et al., 2000; Raymond et al., 2009; Steele et al., 2003) and *in vitro* (Bessemers et al., 2008; Matthys et al., 2007) data in large non-coronary systemic arteries.

In larger conduit arteries, reduced modelling provides valuable insight into the development of methods for the diagnosis of disease (Alastruey et al., 2009a, 2009c; Franke et al., 2003; Stergiopoulos et al., 1992) and the identification of anatomical variations (Alastruey et al., 2006, 2007) by wave analysis. Additionally, it is used to improve the accuracy of the boundary conditions in 3D simulations of localised areas of the vasculature (Formaggia et al., 2001; Papadakis, 2009; Passerini et al., 2009; Urquiza et al., 2006). Huo and Kassab (2007), Smith et al. (2002) and Zamir (1998) applied 1D modelling to simulate pulse-wave propagation in the coronary arteries. However, they did not account for the external pressure produced by the myocardium contraction (Krams et al., 1989b; Spaan et al., 1981), which was simulated in the reduced models by Guiot et al. (1990), Mynard and Nithiarasu (2008), Rammos et al. (1998). Mynard and Nithiarasu (2008) also coupled their coronary 1D model to a 1D model of the non-coronary systemic arteries through a lumped parameter model of flow in the left ventricle and aortic valve.

Any 1D model has to be truncated after a relatively small number of generations of bifurcations. The downstream vasculature is usually simulated using lumped parameter models (Alastruey et al., 2008) or structured tree models (Olufsen et al., 2000) relating pressure to the flow at the outflow of each 1D model terminal artery. Estimation of the parameters of these terminal models can benefit from available morphometric data (Section 2). Lumped parameter models have also been used to simulate coronary blood flow (e.g. Bruinsma et al., 1988; Scheel et al., 1989; Bovendeerd et al., 2006; Jacobs et al., 2008; Algranati et al., 2010).

The 1D formulation has also been used to derive methods for the analysis of *in vivo* pressure and velocity measurements in both the time and frequency domains (Avolio, 2009; van den Wijngaard et al., 2009; Hughes and Parker, 2009). If these measurements are taken simultaneously, it is possible to separate the forward and backward components that make the pulse waveform using wave intensity analysis, which provides valuable information on the conditions of the system upstream and downstream of the measuring site (Parker and Jones, 1990; Parker, 2009) (Fig. 3). This method has been applied to study the effect on the coronary pulse waveform of cardiac pumping and distal vessel compression by the myocardium (Sun et al., 2000, 2004; Davies et al., 2006b; Hadjiloizou et al., 2008). Additionally, the buffering function of the aorta can be quantified by separating the pressure waveform into a space-independent reservoir component that depends on global parameters (cardiac output and total compliance and resistance), and a wave component that changes in time and space according to local properties (geometry and local wall stiffness or compliance): the so-called ‘reservoir–wave separation’ (Aguado-Sierra et al., 2008; Alastruey et al., 2009b; Wang et al., 2003).

4.4.1. Challenges—Reduced modelling has great potential for answering questions on diagnosis and surgical planning that cannot be addressed *in vivo* due to technical and physiological reasons (e.g. some vessels are inaccessible and manipulation of the properties of interest can be dangerous or can elicit reflex compensation). Examples of clinically relevant applications of 1D modelling in the coronary arteries are the detection of microvascular disease in the presence of stenosis by wave analysis, improved understanding of the effect of cardiovascular drugs on coronary flow, and the study of coronary autoregulation.

However, much of our current understanding of coronary and non-coronary haemodynamics is still explanatory rather than predictive. The determination of wave speed in coronary arteries still remains one of the main challenges. It is required to separate waves into forward and backward components (Parker and Jones, 1990) and is one of the key parameters in any 1D simulation. A single-point method was proposed by Davies et al. (2006a) to estimate this speed in humans, but Kolyva et al. (2008) reported complications in applying this method to coronary arteries because of their short length; problems were especially apparent for conditions commonly encountered in the catheterisation laboratory, such as downstream of an epicardial stenosis and in response to pharmacologically induced reduction in microvascular resistance. These complications, however, did not seem to be critical when separating forward and backward travelling waves using clinical data obtained in undiseased coronary vessels at resting flow conditions. Although the magnitude and shape of the forward and backward components changed with wave speed, the integrated forward and backward wave energy was relatively constant (Siebes et al., 2009).

To our knowledge, the 1D formulation has not yet been tested in the coronary arteries against *in vivo* or *in vitro* data without involving parameter fitting. If 1D modelling is able to capture the main features of coronary pulse waveforms, it will be a useful tool to test methods for inferring the properties of the system (such as local wave speed) from *in vivo* data, since these properties are known a priori in a numerical simulation. The development of these methods will also benefit from a full understanding of the mechanisms underlying the simulated wave patterns for a given location within a large network, which is still an open problem. In the coronary arteries myocardial contraction adds an additional complication to this understanding. A recently developed ‘wave-tracking’ algorithm (Alastruey et al., 2009b) may shed some light on understanding these mechanisms. The algorithm allows one to systematically follow all the multiple wavelets that combine to make the observed pulse waveform at an arbitrary measuring site and to identify all the reflection sites that these wavelets have visited. This type of post-processing seems to be

adequate to reduce the datasets generated in simulations with multiple arterial segments and communicate results to a wider (i.e. clinical) audience.

There has been very little research on venous haemodynamics (Uhlir et al., 1984; Kajiya et al., 1985, 1986, 1989). Models of blood flow in arteries cannot be applied to accurately simulate blood flow in veins because of the anatomical and physiological differences between them. *In vivo* data in humans (Cheng et al., 2003) and dogs (Kajiya et al., 1985, 1989; Wang et al., 2006) have shown the pulsatile nature of venous pressures and flows and, hence, the potential of 1D modelling to elucidate the mechanisms underlying venous haemodynamics in coronary and non-coronary circulations (as exemplified by Fullana and Zaleski (2009)). Other directions that reduced modelling might take are the coupling with models of myocardial mechanics (see Section 3), flow regulation (Section 6) and cellular metabolism (Section 8) to further quantitatively investigate blood flow and heart disease.

5. Mass transport processes

5.1. Introduction

As a result of providing continuous perfusion the coronary system arguably fulfills its most central role, to supply the cells of the myocardium with metabolic substrates while washing away metabolic wastes, providing the inputs and outputs for the metabolic processes that drive cardiac electrophysiology and mechanics. Oxygen is an example of a particularly crucial solute: to maintain the energetic state of the heart (and indeed all of the tissues of the body) oxygen must be continuously picked up in the pulmonary circulation, delivered to the left side of the heart, and pumped into the systemic circulation.

In the coronary branches of the systemic circulation, oxygen is highly extracted from the blood. Following a cessation in blood flow, oxidative adenosine triphosphate (ATP) synthesis (and hence cardiac function) ceases within seconds (Wu et al., 2008). Therefore it is not surprising that both acute control of blood flow (Tune et al., 2004) in the myocardium and vascular remodelling are tightly coupled to venous oxygen tension. Yet oxygen is by no means the only important player in the story. Small-molecule signals involved in vasoregulation, such as adenosine, ATP, and NO, are advectively transported in the blood, as are hormones, growth factors, drugs, glucose, fatty acids, carbon dioxide, bicarbonate, immune factors, and much more. Furthermore, local transport of solutes and agonists at the endothelial surface strongly influences endothelial cell biology as a result of the association between these molecules and their endothelial receptors (Dull and Davies, 1991; Mo et al., 1991). Additionally, transport of plasma macromolecules into the wall may be important in the development of atherosclerosis. Experimental evidence shows that such transport can vary spatially at branches of the coronary arteries (Staughton et al., 2007; Kwon et al., 2008). In addition, mass transport is affected by arterial wall disease and wall compression (Stangeby and Ethier, 2002; O'Connell and Walsh, 2010).

Because the processes involved in physiological mass transport (advection, diffusion, permeation, binding, exchange, and reaction) for all of these substances are diverse in terms of their important time and length scales as well as in terms of the underlying mathematics that capture the phenomena, there exists no single appropriate theoretical/computational framework for simulating physiological mass transport. However we can in broad terms explore several important issues for consideration in simulating physiological mass transport, as well as consider the limitations and challenges associated with current technology. In the following sections we illustrate these issues via consideration of oxygen transport.

5.2. Oxygen transport

Simulating the transport of oxygen in the myocardium presents some particularly instructive challenges. First, there is the problem of scale. Oxygen diffusion from microvessels into myocytes is driven by concentration gradients on the scale of the diameter of the myocytes, which is 20 μm or less at typical oxygen consumption rates, as illustrated in Fig. 4. At the organ scale, as shown in Fig. 5, there exist regional heterogeneities in perfusion and oxygen consumption. Thus we are faced with a system that exhibits important three-dimensional structure and heterogeneity from the micron to the centimetre scale. Brute force discretisation is clearly not a feasible approach to capture oxygen transport in the whole heart due to computational intractability.

Modelling oxygen transport in idealised model geometries originated with Krogh and Erlang (Krogh, 1919a). A typical approach adopts Krogh's approximation that each capillary supplies "oxygen independently of all others to a cylinder of tissue surrounding it" (Krogh, 1919a). Advective oxygen transport is simulated in the central capillary and diffusion and metabolic consumption are simulated in the surrounding tissue. While a simple "Krogh cylinder" model cannot capture the micro-scale heterogeneity of oxygenation in the myocardium (Wieringa et al., 1993; Beard et al., 2003), it has been shown that an ensemble of independent blood–tissue exchange units accounting for a realistic distribution of flows and path lengths may (Wu et al., 2008). More sophisticated formal approaches to homogenising micro-scale heterogeneity may prove to be an even more powerful approach (see Section 9.1).

Inherent coupling of transport to other sub-cellular and tissue-level phenomena presents additional challenges. Again considering oxygen, the rate of oxygen consumption is often conveniently represented as a smooth function of oxygen concentration (Popel, 1989). This phenomenological approach facilitates the simulation of realistic oxygen gradients, yet does not represent the link between cellular function and oxidative metabolism that is at the heart of coronary physiology. The mechanistic connection from oxygen to ATP to cellular processes such as contraction and electrophysiology involves a complex network of biochemical reactions (Wu et al., 2009c). Simulating the interplay between blood flow and cellular mechanics, in heart disease for example, will require a reasonable representation of the metabolic network that determines cellular pH and ATP hydrolysis potential as a function of oxygen availability and the kinetics of ATP consuming processes.

5.3. Challenges

Identification of model parameters in transport modelling highlights two related challenges: firstly, to obtain data from experiments designed to identify model parameters; and secondly to estimate parameters based on fitting simulations to the data. Indicator dilution experiments are the basis for one formal and powerful approach. The idea is to observe the outflow kinetics of tracer labelled substances following introduction of the labelled substances into an organ or tissue. Using multiple indicators, it is possible to systematically identify a relatively large number of parameters. For example, 5 parameters underlying intravascular dispersion of substances in the coronary vasculature in a blood–tissue transport model have been identified by fitting the washout curve for an intravascular tracer (Kuikka et al., 1986). Parameters for permeation through endothelial clefts, across endothelial cell membranes, across myocyte membranes, as well as parameters involved in the kinetics of biochemical reactions may be identified based on a series of washout curves for additional substances. In all, more than 10 parameters may be estimated by experiments with three or more tracers (Schwartz et al., 1999).

6. Regulation

6.1. Introduction

Key to efficient mass transport within the coronary circulation, to meet the functional demands of the heart, is the regulation of the transport processes outlined in Section 5. Under normal conditions, the rate of blood flow to tissue is regulated to meet metabolic requirements, particularly oxygen consumption, but is relatively unaffected by changes of arterial pressure. In human myocardium, the oxygen consumption rate varies over approximately a five-fold range between rest and intense exercise, from about 0.1 to 0.5 $\text{cm}^3\text{O}_2/\text{cm}^3/\text{min}$ (von Restorff et al., 1977). Perfusion increases almost in direct proportion to oxygen consumption over this range, and oxygen extraction, expressed relative to convective arterial inflow of oxygen, remains relatively constant in the range 70–80%. Thus, the heart exhibits remarkably efficient metabolic regulation of blood flow. Autoregulation of blood flow refers to the maintenance of almost constant flow in the face of changes in arterial pressure, and the normal myocardium is also very effective in this regard. For example, perfusion is almost constant for variations of arterial pressure in the range 60–140 mmHg (Johnson, 1980).

Local regulation of blood flow is achieved mainly through the active contraction and dilation of small arteries and arterioles, while oxygen exchange occurs primarily in the capillaries. Much can be learned by studying blood flow to intact tissues and organs, but a thorough understanding of flow regulation requires consideration of phenomena occurring at the level of the microcirculation.

The challenge of understanding blood flow regulation has been recognised since the late nineteenth century (Gaskell, 1878). Over the years, many components of flow regulation have been identified and studied in depth. These include autonomic nervous stimuli, circulating substances, mechanical stimulation of vessels, myogenic responses, shear-dependent responses, metabolic responses, conducted responses propagated along vessels, and communication between paired feeding and draining vessels. Such studies have generated a wealth of information on the structure and function of the microcirculation, and on the various mechanisms governing the contraction and dilation of arterioles. (See Davis et al. (2008) for an extensive review).

The ability of the coronary circulation to regulate blood flow according to spatially and temporally varying requirements is fundamental to normal cardiac function, and strongly influences the response of the heart to disease and other perturbations. Many drugs aimed at improving cardiac function are vasoactive. The development of integrated theoretical models, which will allow realistic predictions of cardiac function and responses to various conditions and treatments, must include a quantitative description of blood flow regulation.

6.2. Modelling approaches

Progress in development of a quantitative theory of blood flow regulation has been relatively slow, despite the availability of extensive biological data. Two major obstacles have slowed progress. Firstly, key mechanisms involved in flow regulation remain to be identified. Studies on the response of endothelial cells to changes in wall shear stress have yielded much information about the cellular processes involved, but the fundamental mechanisms by which mechanical stimuli are converted into chemical signals remain unknown (Davies, 1995; Davies and Helmke, 2009). A similar situation holds with regard to the ability of vascular smooth muscle to sense changes in tension or elongation (Davis and Hill, 1999). The mechanisms involved in metabolic control have likewise been difficult to identify (Tune et al., 2004). The lack of specific mechanistic information does not prevent the development of models based on phenomenological assumptions. However, as more mechanisms are

identified and described quantitatively, it will be possible to develop more realistic and reliable models.

A second major obstacle to progress is that the system involves numerous components that are coupled and interact on several levels, making it difficult to isolate and study the components separately. The circulatory system can be regarded as a network of interconnected variable resistances, and changes in the resistance of any one element effect flows and pressures in all segments connected in series or in parallel. Such changes alter the distribution of intravascular pressure and wall shear stress, which then evoke active responses in the cells forming the vessel walls, further altering the distribution of resistance. Information about metabolic and haemodynamic conditions is transferred between tissue and vessels and among vessels by several mechanisms (Secomb and Pries, 2002). More than twenty years ago, it was stated that “A significant remaining challenge is that of integrating observations on small and large vessels into a general picture of flow control” (Duling et al., 1987), and to a large extent this is still true.

A logical response to this complexity is to develop theoretical models for phenomena occurring on the scale of microvessels, and to use these models as a framework for integrating information on the underlying processes and thereby predicting larger-scale behaviour. We have already seen that the value of this approach was recognised by August Krogh, who together with the mathematician Erlang, developed the classic Krogh cylinder model for oxygen transport to tissue (Krogh, 1919a, 1919b) in order to explore the relationship between the number of capillaries in a tissue and the rate at which oxygen can be delivered (refer also to Section 5).

Theoretical models for blood flow regulation were reviewed recently (Secomb, 2008), and some key points from that review will be reiterated here. According to Poiseuille's law, blood flow is proportional to the fourth power of diameter if the pressure drop and other quantities are held fixed. This implies that large changes in flow can be achieved by moderate changes in diameter, and also that control of blood flow requires relatively precise control of vessel diameters. The control of blood flow is primarily achieved by contraction and relaxation of vascular smooth muscle (VSM) in vessel walls. Many factors influence the level of tone generated by a VSM cell, including its length and tension, local levels of metabolites and signalling molecules, communications with other cells via gap junctions, and neural inputs.

Ideally, theoretical simulations of flow regulation should be based on an integrated model for the responses of an individual VSM to all these stimuli. A comprehensive model of this type is not available, but some aspects of VSM responses have been considered theoretically (Gonzalez-Fernandez and Ermentrout, 1994; Yang et al., 2003a, 2003b, 2005). The generation of nitric oxide and other substances by endothelial cells strongly influences VSM tone, and has been modelled theoretically (Chen and Popel, 2006). As yet, work using this approach is at a relatively early stage.

An alternative approach is to develop models to describe the vasoactive behaviour of arteriolar segments (Miller et al., 1997). Some aspects of this behaviour have been well studied in preparations of isolated perfused arterioles. In particular, the myogenic response of VSM to changes in vessel wall tension has been extensively studied (Johnson, 1980), and several theories have been developed (Secomb, 2008). Increased wall shear stress causes vasodilation of blood vessels (Pohl et al., 2000), but relatively few theoretical models have included this effect (Carlson et al., 2008; Cornelissen et al., 2002; Fung, 1997; Liao and Kuo, 1997).

Recently, a potential mechanism of metabolic flow regulation has been described, based on the release of ATP by red blood cells at a rate that depends on haemoglobin saturation in the red cell. According to this mechanism, the red blood cell acts as both a carrier of oxygen and a sensor of oxygen levels (Ellsworth, 2000). Application of ATP to venules has been shown to stimulate upstream conducted responses along vessel walls via the capillaries, leading to arteriolar vasodilation (Collins et al., 1998). The combination of saturation-dependent ATP release and conducted responses initiated by ATP provides a potential mechanism for metabolic regulation of cardiac perfusion (Deussen et al., 2006), although other mechanisms may also be involved (Duncker and Bache, 2008). In a recent theoretical model for metabolic flow regulation and autoregulation based on this mechanism (Arciero et al., 2008; Carlson et al., 2008), a simplified vascular network consisting of seven representative segments is considered, of which two segments, representing the arterioles, are assumed to be vasoactive. Length-tension characteristics of VSM are explicitly considered. The total tension in the vessel wall is expressed as the sum of active and passive components. The active component is proportional to the activation which varies between 0 and 1 and has a sigmoidal dependence on the sum of the stimuli acting to control the tone of VSM, including wall tension, wall shear stress and a metabolic signal. With this model, predicted metabolic regulation and autoregulatory behaviour agree well with experimental data from skeletal muscle and other tissues. The model has not yet been tested using data from the coronary circulation.

6.3. Challenges

Despite the availability of increasing amounts of biological data on individual mechanisms, the key challenge that remains is to develop an integrated understanding of flow regulation. Obstacles have been the lack of mechanistic information on key processes and the complexity of the system. Experimental results obtained during the past decade have suggested a mechanism for metabolic flow regulation in response to blood oxygen levels in venules. As more mechanisms are identified and described quantitatively, the challenge will be to develop more realistic and reliable models. Such models should take into account the intrinsic heterogeneity in the structure of the microcirculation, which causes non-uniform flow distribution. Local flow regulation must result in close matching of flow to metabolic demands despite this heterogeneity (Walley, 1996). If supply and demand are not matched, oxygen extraction from blood is reduced and regional hypoxia may occur. A further challenge in modelling flow regulation is to integrate the intrinsic mechanisms discussed above with the effects of extrinsic factors, including the effects of the autonomic nervous system and of circulating hormones with vasoactive properties such as adrenaline.

7. Angiogenesis and vascular remodelling

7.1. Introduction

On a significantly longer time scale than the regulatory mechanisms discussed in Section 6, the locations of the major coronary vessels are determined by development and remodelling mechanisms. During early development vascular structure is defined by genetic programming. As the heart grows, the development of the vasculature, and especially the large number of vessels forming the microcirculation, is increasingly determined by local responses to a number of feedback signals, including levels of metabolites and growth factors, and mechanical stimuli generated by the blood flow itself (Pries and Secomb, 2008). Even in adults, the vasculature is a dynamic structure, capable of generating new vessels, remodelling existing vessels, and regressing according to changing physiological and pathophysiological conditions (Carmeliet, 2005). For example, the growth of myocardium in response to increased workload must be accompanied by increases in the numbers of microvessels and in the diameters of the major vessels. If some blood vessels are blocked

due to atherosclerosis or thrombosis, the outcome may depend on the ability of remaining vessels to provide blood flow through alternative pathways, forming collaterals (Schaper, 2009).

Improved understanding and quantitative simulation of angiogenesis (the growth of new blood vessels from pre-existing microvasculature) and vascular remodelling (structural changes of existing vessels) including arteriogenesis contributes in many important ways. Quantitative information on the structure of the vasculature is needed as a basis for analysing the haemodynamics of coronary circulation, and also for predicting mass transport characteristics. A number of experimental techniques for determining network structure have been developed (Cassot et al., 2006; Jorgensen et al., 1998; Kassab et al., 1993; Sands et al., 2005): see also the detailed discussion of vascular casting (Section 2.2) and structural imaging of coronary vasculature (in Section 2.3). With these techniques, increasingly detailed maps of vascular structure have been obtained, extending to the microvascular level. However, such studies are difficult and laborious, and are specific to a particular tissue sample. Their value and generality could be enhanced with better understanding of the principles and processes underlying the development of vascular structures. Furthermore, to predict the outcome of diseases and the effects of treatments in the coronary circulation, it will be necessary to simulate structural responses of the vasculature to perturbations and to surgical or pharmacological interventions. For example, with the growing clinical importance of anti-angiogenic drugs comes the need to better understand the cardiovascular side effects of such drugs.

Numerous biochemical and physical factors govern angiogenesis and vascular remodelling. Vascular remodelling includes processes of arteriogenesis and collateral growth important for coronary circulation. Among the biochemical factors are several families of growth factors that stimulate vascular growth: vascular endothelial growth factors (VEGF), fibroblast growth factors (FGF), hepatocyte growth factors (HGF), angiopoietins (Ang), platelet-derived growth factor (PDGF), and transforming growth factor (TGF- β). Other protein families play an important role in angiogenesis and vascular remodelling, e.g. matrix metalloproteinases (MMPs) that have the capacity to proteolyze the extracellular matrix (ECM) and enable new or existing vessels to grow. Hundreds of other molecules have been identified as important participants in the processes of angiogenesis and vascular remodelling. Thus, developing a comprehensive set of computational models at the molecular level describing even the major factors and their interactions is challenging.

Physical forces also play an important role in both angiogenesis and vascular remodelling. The physical forces within the vascular wall include time-dependent shear and pressure forces exerted by the flowing blood, and rhythmic stretching and compressing of the vasculature by the contracting myocardium. Fluid mechanical forces acting on the endothelium are transduced and result in complex signalling cascades in the endothelium and smooth muscle (Valentin et al., 2009; Valentin and Humphrey, 2009a, 2009b). Experiments demonstrate that physical forces differentially affect vascular growth; e.g. elevated static stretching leads to sprouting angiogenesis whereas shear forces lead to splitting angiogenesis (splitting of existing capillary vessels into two) (Hudlicka and Brown, 2009).

Vessels can grow by proliferation of vascular cells and secretion of extracellular matrix components, and by either incorporation of circulating endothelial progenitor cells (EPCs) (Jujo et al., 2008) or recruitment of stromal cells that differentiate into vascular pericytes or smooth muscle cells upon contacting the vessel (Peirce et al., 2004).

7.2. Angiogenesis

Coronary angiogenesis may be a normal physiological process (e.g. as a result of exercise) or pathological (e.g. in a developing atherosclerotic plaque). In many cases, including diseases of ischemic heart and skeletal muscle, angiogenesis occurs in response to hypoxia. A transcription factor, hypoxia-inducible factor, HIF1, acts as an oxygen sensor whose activity leads to upregulation of VEGF secretion from myocytes and stromal cells (Semenza, 2004) that diffuse through the interstitial space and can bind to the endothelial cell receptors VEGFR1 and VEGFR2, initiating a signal transduction cascade that leads to endothelial cell proliferation and migration. The production of matrix metalloproteinases, MMPs, by the endothelial cells is necessary for selective proteolysis of the capillary basement membrane and the ECM, which constitute physical barriers to capillary sprouting. In addition, MMPs release growth factors sequestered in the ECM; they may also uncover cryptic sites of the ECM proteins, a number of which have been identified as anti-angiogenic. Once the catalytic cascade is initiated, a single endothelial cell breaks through the basement membrane and invades the ECM, serving as the tip of an emerging capillary sprout that is followed by proliferating “stalk” ECs (Gerhardt et al., 2003). VEGF also serves as a chemoattractant for the nascent sprout. Multiple capillary sprouts may interconnect leading to the formation of a neovascular plexus. Many of the sprouts will retract; the surviving sprouts undergo maturation and remodelling by recruiting precursors of supporting vascular cells, pericytes and smooth muscle cells, via platelet-derived growth factor, PDGF, secreted by endothelial cells. When the precursor cells make contact with the nascent sprout, transforming growth factor TGF- β acts by suppressing proliferation and migration of the endothelial cell and stimulating differentiation of the precursor cells into pericytes and smooth muscle cells.

7.3. Role of vascular endothelial growth factor family in angiogenesis

The discovery of VEGF-A has led to an exponential growth of publications on angiogenesis and VEGF. Currently, six human alternate splice-isoforms of VEGF-A have been identified: VEGF₁₂₁, VEGF₁₄₅, VEGF₁₆₅, VEGF₁₈₃, VEGF₁₈₉, and VEGF₂₀₉. Binding of ligands to the VEGF-receptors on the surface of endothelial cells originates signal transduction cascades leading to receptor phosphorylation and the resulting increase of vascular permeability, EC cell proliferation, migration, protease secretion and stabilisation of neovessels. The VEGF family members are critical angiogenic growth factors, and are expressed in cardiac muscle, yet the precise role that each of these factors plays is not completely understood. VEGF is necessary for the embryonic development of coronary vessels. Increases in VEGF expression in muscle are linked to, and precede, the increases in vascular density that occur when cardiac muscle is faced with increases in functional demand. VEGF also promotes the activation of endothelial nitric oxide synthase (eNOS) and NO production. Activation of eNOS and generation of NO have been shown to be essential for angiogenesis, and NO production may be a critical step in the mobilisation of repair cells from the bone marrow, which can contribute to angiogenesis and vascular remodelling. Mathematical and computational models of VEGF-receptor interactions *in vitro* and *in vivo* have been formulated in a series of recent studies (Mac Gabhann and Popel, 2008; Stefanini et al., 2008; Wu et al., 2009a, 2009b).

7.4. Role of mechanical factors in angiogenesis

These biochemically regulated pathways are in turn regulated by mechanical forces which are a major determinant of angiogenesis (Ingber, 2002; Milkiewicz et al., 2006; Shiu et al., 2005). Effects of shear forces and stretching have been amply demonstrated at the level of endothelial cells. The forces affect gene expression and intra- and inter-cellular signalling. The interaction of the endothelial cell with its physical microenvironment, particularly the extracellular matrix, impacts the cell function. Mathematical and computational models of

endothelial cell mechanics are under development (Ferko et al., 2007). These developments have yet to be integrated into a molecular- and cellular-based model of a microvessels and its growth.

7.5. Therapeutic angiogenesis in myocardial ischemic disease

Myocardial ischemia is in most cases a consequence of the coronary artery disease; it can be ameliorated by increased blood perfusion of the ischemic tissue. Increased blood perfusion requires both angiogenesis and vascular remodelling. Therapeutic angiogenesis is the induction of microvascular growth aimed at treating patients with inadequate tissue perfusion. Numerous clinical trials for different modes of therapeutic angiogenesis have been conducted in the last two decades; however, at present no therapies are available to increase blood flow to the ischemic myocardium. In some cases, transient increases of perfusion have been achieved, but over time the improvements are lost. Theoretical studies addressing some aspects of therapeutic angiogenesis are emerging (Mac Gabhann et al., in press-a, in press-b).

7.6. Computational models of angiogenesis

Computational and mathematical models of angiogenesis have recently been reviewed (Peirce, 2008; Qutub et al., 2009a, 2009b). Most of the applications of published models deal with tumour-induced angiogenesis (Bauer et al., 2007; Macklin et al., 2009; Owen et al., 2009) and skeletal muscle (Mac Gabhann et al., 2007a, 2007b; Mac Gabhann and Popel, 2007; Peirce et al., 2004). Even though many of the model elements are similar in different organs and tissues, specific modelling of the important area of coronary angiogenesis awaits development. Models at the vessel and network levels consider sprouting angiogenesis; splitting angiogenesis and intussusception as models of angiogenesis have received little attention in theoretical studies.

7.7. Structural adaptation

An early theoretical approach to the problem of structural adaptation was based on an optimality principle (Murray, 1926). As discussed in Section 2.5, the vascular system shows large deviations from Murray's law, and optimality principles, based on minimizing an energy cost, do not necessarily take into account the functional requirements and constraints that apply to the system (Reneman and Hoeks, 2008). Murray's law suggests that the vascular system could achieve an optimum state by adjustments of vascular diameter in response to deviations of shear stress from a set point (Rodbard, 1975). According to this theory, an increase in blood flow in a given vessel triggers increased wall shear stress, leading to enlargement of the vessel, and a return of the wall shear stress to the set point value. Central to this model is the primary regulatory function of the endothelium, the presence of which is essential for physiological acute vasoregulation (Pohl et al., 1986) and critical for (chronic) adaptive structural remodelling (Langille and O'Donnel, 1986).

However, vessels respond structurally to several stimuli besides wall shear stress. Theories including the effects of multiple stimuli have been developed (Pries et al., 1998, 2001, 2005), and recently reviewed (Pries and Secomb, 2008). In these theories, the diameter and wall thickness of each vessel in a network are treated as dynamic variables that change in response to several stimuli including wall shear stress, circumferential wall tension, and levels of metabolites (Hacking et al., 1996). In particular, an increase in intravascular pressure leads to increased tension in the vessel wall. The structural response involves an increase in wall mass through growth and proliferation of smooth muscle cells, and a decrease in the internal diameter of the vessel. An increase in peripheral resistance is a key aspect in the development of hypertension, and reflects inward remodelling of the small arteries and arterioles (Mulvany, 2008). This structural response to increased pressure

produces a positive feedback mechanism, since an increase in peripheral resistance requires increased arterial pressure to maintain flow. Such a mechanism may play an important role in the progressive development of hypertension (Pries et al., 1999). Conversely, prolonged exposure to reduced pressure and low VSM tone, e.g. downstream of a coronary stenosis, may induce outward remodelling (Li and Fung, 2002), which in turn gives rise to impaired autoregulation when distending pressure is suddenly restored by treatment of the stenosis (Verhoeff et al., 2005).

Theories for structural adaptation must also include responses to changing metabolic demands. For instance, chronic hypoxia leads to enlargement of existing vessels, and therefore to increased blood flow. This response is also necessary to stabilise parallel flow pathways which otherwise lead to unstable behaviour (Hacking et al., 1996). A key element is the inclusion of effects of conducted responses that allow propagation of information about tissue metabolic needs upstream to feeding vessels. Without conducted responses, the network is unable to appropriately balance flows in long and short flow pathways (Pries et al., 1998).

7.8. Challenges

The theory for angiogenesis is not at the stage where the formation of microvascular networks can be reliably predicted. Progress has been made in predicting events at the molecular level, e.g. for the VEGF, FGF2, MMP, and HIF1 families, but much remains to be done at both the molecular and cellular levels in describing the effects of other important molecules as well as mechanical forces. Above the cellular level, the theory of network formation has yet to be developed; such a theory will use a combination of the molecular and cellular information and experimentally-derived relationships.

The theories for structural adaptation described above are suitable for inclusion in integrated network-level models for the long-term remodelling of the coronary vasculature. For example, if vascular network structure is known in sufficient detail, it is possible in principle to predict the formation of collateral pathways following the occlusion of an artery (Gruionu et al., 2005a). However, this approach presents several obstacles and challenges. Experimental information on the dynamics of structural adaptation is difficult to obtain, because experimental preparations allowing observation of vascular structure cannot generally be maintained for periods longer than a few hours, with the exception of window chamber preparations. The direct observation of long-term adaptation in cardiac tissue is particularly challenging, except for larger vessels that can be imaged with x-ray contrast media. The theoretical models developed so far do not cover the full range of physiological and pathophysiological states. For instance, ischemia and inflammation may evoke a different set of responses from those occurring in normal tissue (Gruionu et al., 2005b). In vessels with active control of vascular smooth muscle tone, remodelling is closely intertwined with regulation of blood flow (Bakker et al., 2008; Valentin and Humphrey, 2009b). Theories integrating these two processes are at an early stage of development (Jacobsen et al., 2008). In the myocardium, vessels are subjected to a pulsatile mechanical environment unlike that in other tissues, and this may influence remodelling (see Section 3). As yet, available theories do not explicitly link the dynamics of remodelling with effects occurring at the sub-cellular level. Such linking of theories across different physical scales is a particular challenge here as in other aspects of the Cardiac Physiome project (Bassingthwaite et al., 2009).

8. Vascular cellular mechanics

The endothelial cell, located at the blood/vessel interface, has many critical functions which include the maintenance of anticoagulant properties, the physiological control of lumen

diameter (vasoregulation), the regulation of vascular permeability, and mediation of both pathological and protective responses associated with acute and chronic inflammation, wound healing, and major cardiovascular disorders such as atherogenesis (Aird, 2007). Throughout the coronary vascular system the endothelial cell is key to sensing the local fluid mechanical environment and transducing the associated fluid mechanical forces into (bio)chemical signals. Here we focus on the response of the endothelial cell to the local flow environment, and describe how in some arterial sites the flow of non-Newtonian fluid through complex geometries that feature flow separation, oscillatory flow with a reversed component, etc, can initiate a series of events resulting in arterial disease.

8.1. The endothelial cell as a mechanotransducer

The endothelial cell is sensitive to fluid dynamical forces such as shear stress (acting in the direction of the flow) and pressure (acting normal to the wall). Endothelial sensitivity to shear stress is particularly important because communication with underlying smooth muscle cells regulates their vasoactivity, migration, proliferation and synthetic rates. Early studies of endothelial mechanotransduction considered changes in endothelial cell morphology when cultured endothelial cells were first subjected to defined flow (Dewey et al., 1981; Levesque and Nerem, 1985). Many studies quickly followed showing that endothelial signalling pathways respond to changes in fluid shear stress (Davies et al., 1984; Olesen et al., 1988). Major reviews of endothelial mechanotransduction include Davies (1995), Nerem et al. (1998), Shyy and Chien (2002), Resnick et al. (2003), Helmke (2005), Lehoux et al. (2006), Hahn and Schwartz (2009), and Davies and Helmke (2009). Flow influences endothelial biology both by the direct action of haemodynamic deformation forces (principally due to shear stress) on the endothelium itself, and by modifying the local transport of solutes and agonists at the endothelial surface and hence the association between these molecules and their endothelial receptors (Dull et al., 1992; Choi et al., 2007).

The luminal side of the endothelium is exposed to flowing blood, the cell edges are anchored to adjacent cells through junctional complexes, and the abluminal surface away from the flow is attached to a sub-cellular connective tissue matrix through highly regulated transmembrane integrin proteins. The cell cytoskeleton is connected to many cell membrane proteins, and in attached cells exists in a state of intracellular tension or prestress (Ingber, 2008) that is changed by external loading, e.g. flow changes. A local deformation of the luminal cell surface may be propagated near-instantaneously to distant cellular sites via membrane proteins attached to the cytoskeleton and the cytoskeleton itself (Helmke et al., 2001). This process of mechanotransmission results in the heterogeneous distribution of stress to locations of strain concentration in the cell, most notably at cell junctions and sub-cellular adhesion sites (Helmke et al., 2003), known hot-spots of mechanotransduction (Davies, 1995; Shyy and Chien, 2002). Since cytoskeletal deformations are accompanied by instantaneous biochemical signalling at multiple sites of strain concentration throughout the cell, a compelling argument can be made for structural continuity originating at the sites of initial haemodynamics-imposed deformation representing a decentralised mechanotransduction model (Davies, 1995).

Two structures potentially play a key role in the endothelial cell response to its local haemodynamic environment: the glycocalyx surface coating of the cell (Vink and Duling, 1996, 2000; Weinbaum et al., 2007; Reitsma et al., 2007) and the primary cilium which can extend up to several microns into the vascular lumen.

The primary structural components of the vascular endothelial glycocalyx are proteoglycans. The primary core proteins are syndecans and glypicans. Dense arrays of glycosaminoglycan (GAG) polymer side chains are bound to the core proteins. Although it is widely accepted that the structure of the glycocalyx is a dense polymer mesh, direct measurements of

material properties relevant to mechanotransmission and mechanotransduction remain elusive. Weinbaum et al. (2003) proposed that the material properties are determined primarily by the flexural rigidity of the core proteins, which they estimated from the recovery time of the glycocalyx thickness after “crushing” by a passing leukocyte in a capillary *in vivo*. Weinbaum et al. (2003) predict that a wall shear stress of 1 Pa is predicted to cause a 6-nm lateral displacement of actin filaments in the submembranous cortical web. This displacement magnitude is similar to that of the myosin motor step size, implying that the force transmitted from wall shear stress is of similar magnitude to individual actomyosin contraction events. More recently this hypothesis has been extended to propose that the forces transmitted from shear stress cause sufficient deformation that the actin dense peripheral bands in regions near cell–cell junctions interact mechanically like the rubber fenders on bumper cars (Thi et al., 2004). In this model, the submembranous actin cortical web and the dense peripheral bands act as a functional mechanical unit, and force transmission from the cell surface to junctional regions occurs through the cytoskeleton in a manner consistent with a decentralisation distribution throughout the cell.

A large body of experimental data support the hypothesis that the glycocalyx serves to influence force transmission to either local signal transduction complexes associated with the luminal membrane or to dense peripheral bands in the actin cytoskeleton (Vink et al., 2000; Hecker et al., 1993; Pahakis et al., 2007; Florian et al., 2003; Gouverneur et al., 2006; Thi et al., 2004; Yao et al., 2007). Despite criticism of the specificity of enzymes used in many experiments to degrade glycocalyx components, both *in vitro* and *in vivo* analyses place the glycocalyx near the initiation of physiologically relevant endothelial mechanotransmission and mechanotransduction mechanisms. In the near future, inhibition of gene and protein expression of glycocalyx components using genetic intervention is likely to be more revealing of the extent to which this complex surface coat is involved in endothelial mechanotransduction.

Endothelial primary cilia have received much less attention. Mammalian cells including endothelium are capable of expressing a single intermediate filament-rich primary cilium of undetermined function (Kojimahara, 1990). The structures are not obvious in cultured endothelium observed by light microscopy and have not been reported in AFM scans of living and fixed cells. However, they have been identified in corneal vessels by electron microscopy and in cultured human umbilical vein endothelial cells by antibody staining of acetyl- α -tubulin and vimentin. Although the glycocalyx may extend the cell boundary by up to 1 μ m, its distribution generally follows the topography of the cell membrane. In contrast, erect cilia may extend several micrometers into the flow field, where higher velocities will impose a greater drag force. Primary cilia may act as amplifiers to open transient receptor potential (TRP) channels or to transmit stress to cortical (and hence cytoplasmic) cytoskeleton. Exposure of human umbilical vein endothelial cells to laminar shear stress resulted in primary cilium disassembly (Iomini et al., 2004). *In vivo*, endothelial cilia have been mapped to high shear locations in the embryonic chicken cardiovascular system (van der Heiden et al., 2006). Recent *in situ* immunostaining of large vessel endothelium in adult mice has revealed expression of endothelial cilia restricted to sites of flow disturbance (van der Heiden et al., 2008). This distribution and the induction of arterial endothelial cilia by the experimental creation of flow disturbance (low and disturbed shear stresses) have led to the proposal that primary cilia act as fluid shear stress sensors in endothelium. The mechanical properties of cilia, a critical consideration for flow mechanotransduction, are unstudied. Further mechanistic evidence of cilium-mediated mechanotransduction using genetic manipulation will help evaluate the role of these structures in arteries to provide a better basis for modelling at the sub-cellular level.

In developing theoretical models for mechanotransduction, the material properties of the endothelium can be described by constitutive equations. Stress–strain relationships range from linear visco-elasticity models of individual elements in series or in parallel to complex moduli that include changes in material properties as a function of stress or strain history (Davies and Helmke, 2009). Measurements of stress–strain relationships are ideally made in living cells, although measurements using gels of cytoskeletal proteins are also instructive (Janmey et al., 1991, 1998). For example, filamentous actin, a prominent cytoskeletal element, can be represented to a first approximation as elastic, whereas intermediate filaments exhibit both creep and strain hardening properties, while microtubules exhibit slow creep.

Many potent labile molecules are present in the cell-free fluid phase close to the endothelial surface (referred to as the boundary layer). These molecules are subject to convective transport that affects their integrity and receptor binding. *In vivo*, bulk flow of blood plasma is excluded from the glycocalyx, as demonstrated by near-wall microparticle image velocimetry (μ -PIV; Smith et al., 2003), and the presence of the endothelial cell glycocalyx further complicates modelling solute transport to receptors at the endothelial plasma membrane (Pries et al., 2000; Weinbaum et al., 2007). The best studied example are probably adenosine nucleotides (ATP, ADP, adenosine) which together with flow have been shown to influence endothelial calcium responses (Dull and Davies, 1991) and autocrine signalling in epithelial cells (Tschumperlin et al., 2004); the glycocalyx has been lumped into these and similar transport models. Since potent degradative enzymes at the endothelial cell surface can destroy ATP, a combination of flow and enzyme activity regulates the concentration of ATP in the boundary layer and limits access to its receptor. The concentration of ATP in the boundary layer is likely to vary widely as a result of the complex flow fields that are encountered *in vivo* and this, plus differential transport in a heterogeneous glycocalyx, may account for the differential signal transduction responses that are observed in the endothelium.

8.2. Mechanotransduction and disease

Within the normal physiology of the heart, structural and functional cell and tissue heterogeneities can increase the probability of later cardiovascular disease. However, beyond overt structural defects are more subtle heterogeneities of arterial geometry that, by creating local flow disturbances, promote athero-susceptible pro-pathological endothelial cell phenotypes before any pathological changes are detectable.

As discussed from a fluid dynamic perspective in Section 4.3, the geometry of the major arteries is key in determining coronary artery flow dynamics. Flow modelling studies link regions of flow separation and flow reversal to the preferential susceptibility for the development of atherosclerotic lesions, the major underlying cause of most coronary vascular disease. Fig. 6 shows endothelial cell 2-D morphology in locations where there is unidirectional laminar flow (most arterial regions; Fig. 6A,B) and where there is significant flow separation with transient flow reversals (branches, curves; Fig. 6C,D). In the latter regions, the cell morphologies undergo a distinct change from normally aligned endothelial shape to a polygonal morphology without preferential orientation. This reveals important changes in the local flow characteristics. For example in the aortic arch inner curvature and regions of the coronary arteries proximal to branches there are significant regions of polygonal-shaped endothelial cells also observable by simple nuclear staining (Fig. 5D). Downstream and distal to the branch points, a transition back to aligned cells defines regional morphological boundaries that likely reflect distinct haemodynamic characteristics (and regions of differential endothelial phenotypes). In studies of cultured endothelium that was induced to assume similar 2-D outlines by flow, Barbee et al. (1994) demonstrated by atomic force microscopy that the topography of the cells is flattened when the cells are

aligned. Since the 3D topography is the flow interface, these surface topography differences have important implications for mechanotransduction at the sub-cellular scale (Davies et al., 1995) and perhaps also for convective mass transfer characteristics (Hillsley and Tarbell, 2002).

In flow separation a volume of blood separates from the bulk flow to form a vortex because of a pressure gradient induced by local changes in the vessel geometry. Because blood flow is pulsatile in large elastic and muscular arteries, the vortex may collapse in diastole and reform during systole Steinman and Taylor (2005). The important haemodynamic characteristics of such complex separation regions are that there is a phase of flow reversal with steep temporal and spatial gradients that creates oscillatory haemodynamic forces; the Oscillatory Shear Index, OSI, is a composite measurement of this. OSI is the fraction of total flow volume (or 2-D section thereof) that reverses during a single cardiac cycle (Suzuki et al., 1998). In flow separation regions the average shear stress is lower and the particle (and solute and blood cell) residence time is increased. Consequently the mechanical and fluid transport environment of endothelium at OSI sites is substantially different; this is reflected in the local endothelial morphology and the athero-susceptible biological phenotype.

Obstruction of blood flow in the coronary arteries, caused by atherosclerosis and/or atherothrombosis, has devastating effects upon large downstream regions of coronary perfusion resulting in angina, vasospasm, and heart attack. Regions proximal to branches are more susceptible to atherosclerosis than more distant sites; for example the proximal flow entry regions of the left and right coronary arteries, the left coronary artery branching region to the circumflex and left anterior descending (LAD) arteries, and major bifurcations within these arteries. The regions where the epicardial portions of the coronary arteries enter the deeper myocardium are also susceptible regions. Arterial geometry at most of these sites results in flow separation during at least part of the cardiac cycle. Most experimental investigations have been conducted on more accessible flow disturbance-vascular susceptibility relationships in arteries outside of the heart (Ku and Giddens, 1983; Davies et al., 2002) but recent genomic investigations of the endothelium (Passerini et al., 2004; Davies, 2009; Civelek et al., in press) indicate that mechanisms uncovered in the non-cardiac circulation are also applicable to the coronary circulation.

Separated flow generates complicated spatio-temporal shear-stress gradients that directly affect the biology of the endothelium. The local haemodynamic environment influences endothelial gene and protein expression, post-translational events, and cell function through a combination of biomechanical and transport mechanisms. Passerini et al. (2004) reported the first high throughput genomic analyses of endothelial cells in the aortic arch (which exhibits, for example, flow separation, flow reversal, low average shear stress, OSI) compared with endothelial cells subject to undisturbed flow in the nearby descending thoracic aorta. There was differential expression of many genes associated with both pro-inflammatory (athero-susceptible) and anti-inflammatory pathways, pro- and anti-coagulation mechanisms, and cholesterol balance, revealing a heightened upregulation of checks and balances in the endothelium of athero-susceptible regions. There was no evidence of pathological changes in the vessel wall in these regions of susceptibility nor were any of the cardinal markers of inflammation expressed. A working interpretation is that cells in disturbed flow regions may be sensitised to additional factors that promote atherogenesis (hypercholesterolemia, hypertension, diabetes, smoking, etc) compared to cells in protected locations. Some insight into the underlying mechanisms that may promote the phenotype differences has recently come to light from studies of the endoplasmic reticulum (ER)-stress response in endothelial cells (Feaver et al., 2008; Zhang et al., 2009; Civelek et al., in press). These studies implicate disturbed flow as a regulatory factor in which the endothelium appears to be subject to a biomechanical form of stress (as compared

with other forms of stress) that results in the chronic activation of the ER-stress response and the adaptive unfolded protein response mechanism. Indeed complex shear stress, such as occurs in flow separation regions, invokes intracellular metabolic stress as a coping mechanism and this state is related to athero-susceptibility. A post-transcriptional pathway mediated by small microRNAs has recently been reported in athero-susceptible endothelium to regulate upstream elements of the pro-inflammatory NFkappaB pathway (Fang et al., 2010).

The association of disturbed flow and reactive oxygen species (ROS)-related genes is a recurrent finding in endothelial genomic analyses. For example, the residence time of superoxide anion, a damaging free radical, is increased at sites of disturbed flow. ROS can induce ER-stress but it is unclear how these mechanisms are linked together in disturbed flow. ROS is clearly present in higher concentrations in disturbed flow arterial regions (Davies and Civelek, in press), and this may impact glycocalyx integrity (van den Berg et al., 2006; Vink et al., 2000).

Another signature of flow disturbance *in vivo* is a decreased availability of nitric oxide caused by downregulation of endothelial nitric oxide synthase (eNOS, NOS3) (de Nigris et al., 2003; Passerini et al., 2004). Since steady undisturbed flow is known to upregulate eNOS (Boo et al., 2002), it is likely that the disturbed flow characteristics are responsible for eNOS downregulation in these regions *in vivo*.

8.3. Challenges

The incorporation of cell-scale modelling into models for the coronary vasculature is an exciting challenge that will benefit from a number of developing ideas and technologies.

A wealth of descriptive detail is emerging that better defines endothelial heterogeneity based on histology and immunohistochemistry in which care is taken to retain spatial relationships; however, information available by this approach is at best semi-quantitative. High throughput approaches are increasingly useful because they carry a large bioinformatics data load that can more readily be imported into systems modelling. Other quantitative approaches might be considered include: (i) the refinement of regional heterogeneity to single cell measurement of candidate gene expression; (ii) site-specific endothelial ROS levels (visualised by dihydroethidium); (iii) activities of key endothelial enzymes in geometrically-defined locations of coronary arteries; and (iv) more sophisticated proteomic/mass spectrometry technologies of spatial quantitation. In pathogenesis, a major challenge is the accurate measurement of endothelial phenotype(s) overlying developing lesions, which presents a non-trivial problem of accessibility, cell isolation and nucleic acid purification.

In addition to determining the effects of heterogeneity higher resolution imaging of flow characteristics is also required for advancing both models and understanding of endothelial function. The localisation of flow disturbances needs to be better defined and at higher resolution. Current methods range from model simulations based upon vascular casting, imaging by MRI and ultrasound, and by directly looking at the morphology of the endothelial cells (e.g. Fig. 6). The latter method is simple but informative (Davies and Bowyer, 1975; Nerem et al., 1981). The latter method is simple but informative. In locations where there is significant flow separation with flow reversals, the normally aligned endothelial shape is lost and a polygonal morphology exists; i.e. the cell reveals important changes in the local flow characteristics (see Fig. 6). For example the aortic arch inner curvature and regions of the coronary arteries proximal to branches there are significant regions of polygonal-shaped endothelial cells (observable by simple nuclear staining for orientation). Downstream and distal to branch points, a transition back to aligned cells clearly defines morphological boundaries that likely reflect distinct haemodynamic

characteristics (and regions of differential endothelial phenotypes). While great improvements in 3D imaging and computational flow modelling of arteries is occurring (e.g. Steinman and Taylor, 2005; Markl et al., 2009), the resolution falls short of that required for cellular/sub-cellular modelling.

Finally, we also need a better characterisation of stenotic lesions and their haemodynamic impact. While the fundamental relationship between arterial stenosis geometry and the resulting pressure drop–flow relationship developed by Young (1979) was also shown to hold for coronary arteries in animals and patients (Gould, 1985), assessing the physiological severity of an obstructive lesion remains a key problem in clinical practice. Cardiologists are frequently faced with multiple non-obstructive lesions and need to decide on the optimal treatment strategy. Modelling of fluid dynamics associated with serial lesions, their location and morphology has the potential to help with decision-making in the catheterisation laboratory. In addition, plaque composition and configuration has been shown to directly influence the risk of rupture, leading to acute and often devastating coronary events. Novel imaging methods such as optical coherence tomography and near infrared spectroscopy can support the clinical assessment of such vulnerable plaques (Narula and Strauss, 2007; Schuijff et al., 2009). Risk stratification and patient management may also substantially be aided by FSI models of unstable plaques. Finally, the perfusion provided by collateral vessels is not well understood and largely dependent on indirect assessment that is not yet well supported by appropriate models (Spaan et al., 2006).

9. Integrated model development

The aim of the Cardiac Physiome project is to simulate the normal and pathophysiological function of the heart, and to understand how clinical interventions and drug therapies may be used to treat the diseased heart. Models are needed for the key components of the coronary vascular system, including structure, biomechanics, flow, mass transport, regulation and remodelling, and cellular responses. However, physiological processes involve many interactions between these basic components, as illustrated by the preceding sections. The challenge then is to develop modelling frameworks within which these components can be integrated, to allow predictions of cardiac function, (compensatory) responses to disease conditions, and optimal treatment strategies.

The models for these components involve descriptions of biochemical and biomechanical phenomena occurring at multiple temporal and spatial scales, including the molecular, cellular, vascular, tissue and organ levels. In integrating these components we are therefore faced with the challenge of combining models at disparate scales. A wide range of theoretical and numerical tools can be used in the development of such multi-scale models, including cellular automata, agent based modelling, stochastic processes, continuum mechanics, compartmental models, multi-phase flows, computational fluid and solid dynamics, many of which have been discussed above.

The challenge is to introduce small-scale information into larger-scale models without the resulting models becoming computationally intractable. One approach is to use a lumped representation of where vessels smaller than a certain size are represented by a single compartment of fixed resistance and uniform properties. This approach is appropriate in many situations and has the advantage of simplicity. However, a limitation of this approach is that significant spatial variations may exist within this compartment, which are not represented by the model.

An intermediate approach between detailed representation of every vessel and a lumped approach is provided by homogenisation theory. In this theory, a local spatial averaging of fine-scale structure is achieved by exploiting asymptotic techniques to estimate tissue-scale

properties, based on explicit solutions in smaller-scale subunits. The approach relies on the separation of the system into disparate length scales; in the simplest case this could be a repeating micro-scale where the structural detail is visible, and a tissue-scale where only the averaged properties are identifiable.

9.1. Homogenisation

Homogenisation theory is in the early stages of being applied to answer specific questions on cardiac function or treatment strategies (see Section 3.2). To illustrate the potential of the homogenisation approach, it is relevant to consider related work modelling perfusion in vascular tumours (Chapman et al., 2008; Shipley and Chapman, 2010). The approach assumes a periodic micro-structure with Stokes flow in the capillaries, Darcy flow in the interstitium, and leakage through the vascular walls; the resulting equations comprise a double porous medium with coupled Darcy flow through the interstitium and vasculature. The Darcy fluid permeability tensors capture the dependence of tissue-scale perfusion on the micro-scale flow characteristics. One advantage is that the effective equations are derived without prescribing the micro-scale structure so that the impact of different network topologies can be tested a priori. Also, the final equations are computationally efficient to solve compared to numerical solutions of the full capillary network.

In addition to fluid transport, such an approach to homogenising micro-scale structures may prove powerful in describing transport of oxygen (and other solutes) within the heart. In the context of tumour modelling, Shipley and Chapman (2010) illustrate how such techniques can be used to model substrate transport, for a range of micro-scale transport properties. When employed in heart modelling, such methods have the potential to overcome the limitation of “Krogh cylinder” models (Section 5.2).

However, the current framework faces significant challenges if it is going to capture the cardiac vasculature in a physiologically realistic way. First of all, the vasculature is a continuous hierarchy of vessels arranged in a complex 3D topology that is not captured by micro and tissue length scales in real space. One possible approach is to discretise the vasculature into units categorised by vessel dimensions, and to move up the length scales using homogenisation: for example, Shipley et al. (submitted for publication) divides the vasculature into capillaries, arterioles and venules. It is essential that any such approach is motivated directly by vascular imaging data, validated against perfusion data, and is applied in topological space to realistically account for the intricate structure of the coronary vascular tree. Secondly, the current framework depends on the leakiness of vessel walls in tumours to correlate vessel and interstitial pressure fields at nearby spatial locations; this vessel leakiness makes spatial averaging a natural choice for tumours. However, the vessels of the myocardium are non-leaky, and this exacerbates the challenge of identifying a meaningful averaging approach. Finally, the models thus far are fixed in time, whereas realistic models of cardiac behaviour must account for time-dependent changes in the vascular structure in response to regulation, angiogenesis, vascular remodelling and myocardial contraction. The functional parameters characterising these processes show large heterogeneity on a wide range of spatial scales, and homogenisation theory will require further development to take account of the interplay between these spatial and temporal effects.

9.2. Integration

Coronary artery disease is a multifaceted problem that involves not only the micro-scale environment of the arterial wall but has far-reaching consequences for perfusion of the downstream myocardial tissue, which eventually degrades myocardial function and cardiac performance. This in turn can negatively influence the conduction system, cardiac

contraction patterns, and thereby coronary flow. Compensatory physiological mechanisms are an integral part of the disease process that need to be taken into account in order to arrive at a complete picture of coronary vascular disease. The link to clinical applications invariably needs to include patient-specific anatomical models and additional structural and biochemical parameters that are as yet difficult to acquire *in vivo*. A key challenge for the near future is to develop a suite of tools that can be adopted in a healthcare environment. The translation of computational physiological models to clinical applications is a key goal of the physiome approach (Brook and Waters, 2008; Hunter and Viceconti, 2009; Popel and Hunter, 2009; Miller, 2010).

The integration of models for multiple processes, presents additional challenges in terms of handling and processing large heterogeneous datasets, and managing and interfacing software implementations of model components. The wider research community will benefit from the establishment of an effective infrastructure for sharing and disseminating the acquired research outputs. Future efforts should be aimed at developing common image and model data standards, tools for processing, visualisation and analysis, and publicly-accessible repositories that will facilitate quantitative modelling investigations. Due to the rapid advancements in acquisition speed and the size of the datasets, e.g. high-resolution imaging data may typically be several gigabytes in size, manual analysis has become impractical. The design of efficient and reliable automated analysis and visualisation algorithms remains a constant challenge for the future, and will benefit from cross-disciplinary research and application of emerging technologies such as GPU computing. In addition, public databases for sharing these raw data and reconstructed models with the wider research community must be established. Some initiatives have been made in this direction (e.g. euHeartDB, <https://euheartdb.physiomeproject.org/welcome.do> Gianni et al. (2010)). These issues of integration and multi-scale modelling are recurrent issues encountered with the Physiome framework, and are not unique to the coronary vasculature (Brook and Waters, 2008).

As illustrated in this review, progress has been made in many areas of theoretical modelling of coronary vascular biomechanics. To realize the full potential of these advances, and to contribute substantially to medical progress, much more work is needed in the development of models for various aspects of the coronary circulation and their integration into models with predictive capabilities. These areas offer many exciting avenues and challenges for future research.

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Fig. 1. Examples of typical length and time scales encountered in constructing models of the coronary vascular system.

Fig. 2.

(a) Reconstruction of the rat coronary vessels from micro-CT (Lee et al., 2007) (color indicates vessel radius, ranging up to 100 microns – comprehensive descriptions of the network morphology can be found in the original publication). (b) Synthetic coronary network (Smith et al., 2000), generated using data from Kassab et al. (1993) to represent the largest six orders of the coronary arterial tree.

Fig. 3.

Catheter-based simultaneous measurements of pressure (P) and velocity (U) in the human circumflex artery (top) and wave intensity results of the separated forward – (dI_+) and backward – (dI_-) travelling waves (bottom). dI_+ are always positive and originated proximally and dI_- are always negative and originated distally. Forward compression waves and backward decompression waves filled in black; forward decompression waves and backward compression waves filled in white. (Modified from Davies et al. (2006b).)

Fig. 4. Spatial heterogeneity and scales of oxygen transport. Simulated spatial distribution of oxygen partial pressure in skeletal muscle, at the microvascular scale, adapted from Tsoukias et al. (2007) with permission. A color scale is used to represent pO₂ in capillaries and in 4 planar cross sections. (Scale bar is approximately 100 μ m).

Fig. 5. Regional heterogeneity in cardiac oxygen consumption, estimated from analysis ^{11}C -acetate PET imaging of in a human heart before and after cardiac resynchronization therapy (CRT), from Lindner et al. (2005) with permission. Color bar indicates regional O_2 consumption in min^{-1} .

Fig. 6.

Arterial endothelial morphologies *in situ* reflect local haemodynamics. A: In pulsatile but unidirectional laminar flow in the descending thoracic aorta, endothelial cells are aligned in the direction of flow (arrow), a morphology that is present in most regions of the arterial circulation. B: The nuclear orientation in a similar region also indicates alignment. C: Cell shape transition region adjacent to an intercostal branch of the aorta where flow separates and reverses during part of the cardiac cycle. Cell alignment (top left corner of image) changes to unaligned polygonal-shaped endothelial cells (right corner). The curved arrows mark a haemodynamic transition zone a few cells wide. Polygonal and randomly oriented cells are associated with arterial branch sites, curvatures and bifurcations that are regions susceptible to atherosclerosis. D: At the athero-susceptible inner curvature of aortic arch, endothelial nuclear shape is representative of a similar disturbed flow region. In A and C the cell shapes are outlined by silver proteinate deposition and observed by scanning electron microscopy (Davies and Bowyer, 1975). In B and D, the nucleus is stained with DAPI and observed by fluorescence microscopy. The latter technique allows rapid evaluation of cell alignment (within several minutes after opening fresh arterial tissue). Nuclear orientation and cell shape are closely correlated. Scale bar = 20 μm . From: Davies, P.F., 2007. In: Aird, W.C. (Eds.) 'Endothelial Biomedicine; A Comprehensive Treatise', Cambridge University Press, pp. 230–245, with permission.