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Review

3D Imaging of vascular networks for biophysical modeling of perfusion distribution within the heart

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ABSTRACT

One of the main determinants of perfusion distribution within an organ is the structure of its vascular network. Past studies were based on angiography or corrosion casting and lacked quantitative three dimensional, 3D, representation. Based on branching rules and other properties derived from such imaging, 3D vascular tree models were generated which were rather useful for generating and testing hypotheses on perfusion distribution in organs. Progress in advanced computational models for prediction of perfusion distribution has raised the need for more realistic representations of vascular trees with higher resolution. This paper presents an overview of the different methods developed over time for imaging and modeling the structure of vascular networks and perfusion distribution, with a focus on the heart. The strengths and limitations of these different techniques are discussed. Episcopic fluorescent imaging using a cryomicrotome is presently being developed in different laboratories. This technique is discussed in more detail, since it provides high-resolution 3D structural information that is important for the development and validation of biophysical models but also for studying the adaptations of vascular networks to diseases. An added advantage of this method being is the ability to measure local tissue perfusion. Clinically, indices for patient-specific coronary stenosis evaluation derived from vascular networks have been proposed and high-resolution noninvasive methods for perfusion distribution are in development. All these techniques depend on a proper representation of the relevant vascular network structures.

1. Introduction

Over the past 20 years, the technical advances in experimental physiology and imaging capabilities have vastly increased the quantity and quality of anatomical and physiological data. The concomitant steep rise in computational power and numerical techniques has enabled multi-scale biophysical modeling of organ function (Hunter and Borg, 2003; Bassingthwaighte and Chizeck, 2008). Apart from integrative modeling of normal physiological function, these studies also aim to understand mechanisms in pathological conditions such as atherosclerosis (Krams et al., 1997), cardiac disease or tumor perfusion and to predict the effect of interventional treatment. Integrative modeling of the heart ranges from subcellular mechanisms and cardiomyocyte electrophysiology (Noble, 2002; Bassingthwaighte and Vinnakota, 2004) to whole heart mechanical and perfusion simulation (Smith et al., 2011).

Blood flow to the myocardium is distributed via the coronary arteries that comprise a densely branching network of blood vessels embedded in the contracting cardiac muscle. Myocardial perfusion is profoundly heterogeneous at multiple spatial scales due to heterogeneity in local oxygen consumption and the asymmetric branching of the intramural vascular tree. Normally, the coronary circulation is capable of matching blood flow to elevated metabolic demand by adjusting vascular tone (Chilian, 1991). At maximal vasodilation, coronary flow becomes dependent on perfusion pressure and coronary resistance is essentially determined by microvascular structure (diameter and length) rather than function (tone). The impeding effect of cardiac contraction on blood flow in coronary resistance vessels results from a combination of mechanisms including local tissue pressure and time-varying muscle stiffness (Westerhof et al., 2006; Spaan et al., 2008). A major consequence is that coronary blood flow occurs predominantly during diastole when the heart muscle relaxes. The dynamics of the contraction process also introduce a transmural gradient in tissue pressure, which is high at the subendocardium and declines toward the epicardium (Hoffman and Buckberg, 1975; Hoffman and Spaan, 1990; Camici and Crea, 2007). As a result, tissue closer to the left ventricular chamber is

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more susceptible to ischemia than the outer myocardial layers. The coronary vascular network is designed to compensate for this impediment by a larger number of subendocardial arterioles (Wusten et al., 1977). However, in conditions that lower perfusion pressure (epicardial stenosis) or shorten diastolic duration (elevated heart rate) the subendocardium will be jeopardized because its flow reserve is exhausted sooner (Merkus et al., 2001; Fokkema et al., 2005).

All modeling efforts of organ perfusion share the common need for a proper definition of the arterial vasculature within the tissue. Early models of vascular networks were based on generic topological properties rather than actual network reconstructions. In order to arrive at a realistic tree structure, the arterial system has to be visualized in three dimensions, 3D, so that arterial segments, their topology and geometry can be quantified. Validation of model-based prediction of perfusion requires methods to accurately measure tissue perfusion distribution in relation to vascular structure. This paper aims to give an overview of the challenges associated with collecting experimental data needed as foundation for model development on tissue perfusion in the heart and validation of these computational models. It is structured accordingly along the following outline; vascular tree visualization techniques, analysis and modeling, determination of tissue perfusion and flow model development for clinical applications.

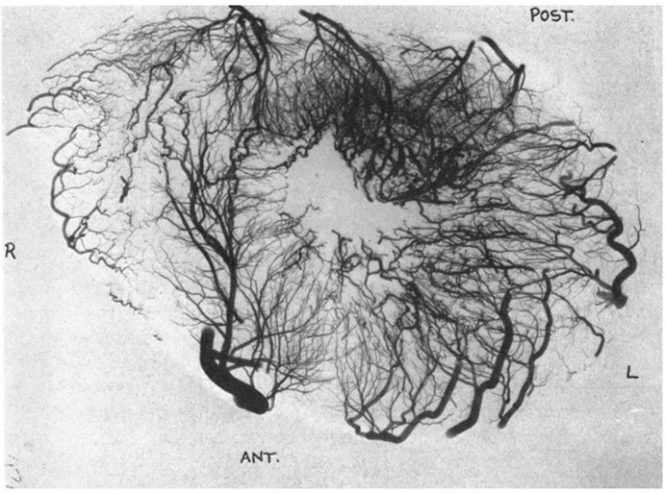

Fig. 1. Ex vivo arteriogram of a short axis slice of a human heart, after filling the coronary arteries with bismuth–oxychloride–gelatin. Ischemia led to a strong increase in vascular density in the posterior wall of the left ventricle by formation of coronary collaterals, with enlargement of deep, subendocardial anastomoses. Branches of the unobstructed left circumflex artery can be seen on the right hand side of the illustration. Reproduced with permission from Fulton (Fulton, 1964).

2. Vascular tree visualization techniques

As early as the second century, Galenius (129–200) described the existence of venous and arterial pools of blood and reasoned that blood was created in the liver and consumed by other organs. It was not until several centuries later that the existence of an actual blood circulation and perfusion of organs was postulated by Harvey (1578–1657) in his "De Motu Cordis". Harvey's conclusion was essentially based on a model interpretation of arterial and venous compartments and the communication between them, since it was not possible at that time to visualize capillaries. Precise vascular morphology in humans remains the realm of post-mortem investigation. Ruysch (1638–1731) conducted numerous studies using vascular infusions with colored liquid media so that at dissection, arteries could be traced throughout the body and organs. In 1857, Virchow succeeded in visualizing very fine details, including arterioles and capillaries of the kidney, by injecting a colored liquid which was subsequently cleared by gradual increase in alcohol concentration (Virchow, 1857). Since then, different kinds of colored vascular casting have been used extensively in physiological research, with applications ranging from the detection of coronary collateral arteries (Baroldi et al., 1956) to vascular anastomoses in placentas (van den Wijngaard et al., 2007).

In this review we focus on studies aiming at visualization of vascular beds of organs allowing functional vascular network analysis. Imaging techniques with a rather limited field of view or superficial penetration such as intravital multiphoton laser scanning microscopy, optical coherence tomography, and orthogonal polarization spectral imaging have recently been reviewed elsewhere (Kiessling et al., 2010). Systems combining noninvasive functional imaging information with structural information from computed tomography in small animals were also recently reviewed (de Kemp et al., 2010).

2.1. X-ray angiography

The first x-ray angiograms demonstrating coronary collateral vessels were produced by Schlesinger in 1938 who filled ex vivo coronary vessels with a radiopaque contrast medium (Schlesinger, 1938). In the 1950s, Fulton used post-mortem stereo-angiography in preserved human hearts to visualize coronary arteries down to several tenths of millimeters in diameter (Fulton, 1956, 1964). He demonstrated extensive superficial and deep intercoronary anastomoses, which were particularly abundant in the interventricular septum and in the subendocardial plexus of the left ventricle. These images gave a good impression of the intricate course of the smaller coronary arteries and identified extensive intercoronary anastomoses (Fig. 1). The technique was subsequently used by Schaper and co-workers to examine coronary collateral formation in the dog in response to timed coronary artery occlusion. These landmark studies identified the role of coronary collaterals in protecting myocardium against ischemia and the role of fluid shear stress in driving collateral vessel outward remodeling (Schaper et al., 1979a, 1979b).

Although these angiographic techniques yielded important morphological information, the essentially two dimensional, 2D, images were not amenable to 3D modeling.

2.2. Vascular casting

Vascular casting opened the road to 3D visualization of the arterial tree. This technique involves the cannulation of the feeding artery of the vascular bed, the removal of blood by flushing with buffer solution and the infusion of a replica material that polymerizes over time. The intramural vessels of the cardiac muscle were studied in different ways. Bassingthwaighte et al. used a silicone elastomer to fill the coronary microcirculation of the dog heart and made the tissue transparent by prolonged immersion in ethanol and methyl salicylate at increasing concentrations (Bassingthwaighte et al., 1974). These authors demonstrated the continuity of the capillary bed over several centimeters with many interconnections between parallel running capillaries, resulting in unbranched capillary segments with an average length of 100 μm. These replicas yielded an excellent overview of the capillary bed and its connection to arterioles and venules. However, the density of the capillary bed is so high that the depth of view was limited to less than 1 mm in most places.

Corrosion casting is a different technique to re-create the intra-organ vascular network, by which high-quality physical replicas of the vasculature are obtained after removal of the surrounding tissue by maceration with a concentrated base or acid (Baroldi et al., 1956).