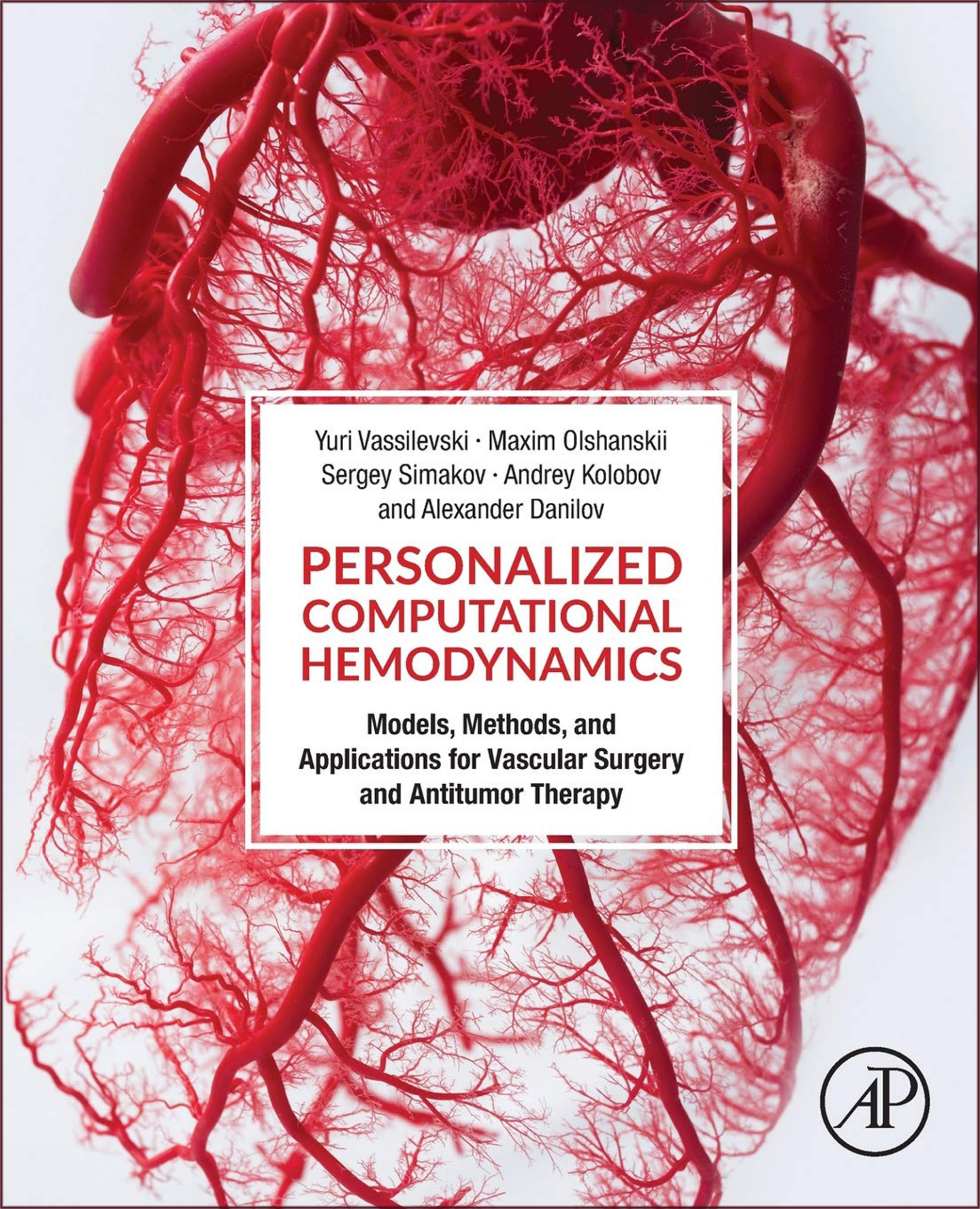

Yuri Vassilevski · Maxim Olshanskii
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PERSONALIZED COMPUTATIONAL HEMODYNAMICS

Models, Methods, and Applications for Vascular Surgery and Antitumor Therapy

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CHAPTER 1

Introduction

Cardiovascular system functionality and disease is a core area of medical research due to its impact on the health and wellness of society. Because of its complexity, the understanding and predictive modeling of cardiovascular phenomena requires joint efforts of physicians, engineers, mathematicians, and scientists working in other fields. As a result, over the past few decades, the area became truly interdisciplinary. This book focuses on the mathematical and computational modeling of the blood flows in the heart, arteries, and microcirculatory networks and interactions of blood flow with the surrounding elastic tissues. An emphasis is made on personalizing the models to a specific patient, since the factors to be accounted by the models vary dramatically depending on the individual physiology and health status. Based on the collaboration with medical doctors from the Institute of Personalized Medicine at Sechenov University, a significant part of the book addresses the application of the mathematical and numerical methods to the predictive treatment of cardiovascular pathologies and the optimization of antitumor therapy.

There exists a huge body of literature on the mathematical and computational modeling of cardiovascular system, which includes several recent monographs [1–6]. The bibliography section of this book lists hundreds of references, still a small subset of the existing literature. Distinct features of this book are (1) a concise but rigorous coverage of fundamental principles and equations of mathematical hemodynamics with a smooth passage to concrete applications in vascular surgery and oncology; (2) a focus on the patient-specific modeling; and (3) an explanation of numerical algorithms in sufficient detail to have the complete modeling cycle presented in one place. The thrust of the book is to provide in one place all of mathematical models, a patient-specific tuning up of the models, and examples of practical applications. Therefore, applied mathematicians, biomedical engineers, and medical doctors will find this book useful for research, diagnostics, and therapeutics.

The book consists of 10 chapters. Chapter 2 gives basic knowledge about human cardiovascular system. The structure of the system and its main parts, the heart, and the vessels network are introduced with necessary details. We discuss the main physical and chemical characteristics of the blood, which affect its circulation. Electrical activity of the

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heart, other major phenomena, and conditions of normal functioning are reviewed before the chapter proceeds to the discussion of some pathological conditions, which are further addressed in the modeling and computational sections of the book. Mathematical descriptions of the cardiovascular system inevitably deal with generic shapes and complex three-dimensional geometries. Acquiring the geometrical information from clinical data such as medical images is a part of the modeling process. Chapter 3 introduces acquisition techniques, methods to represent the image data sets and basic operations with images. Further we go into details of medical image segmentation, which is applied to extract specific information about particular organs or their parts such as the heart cavities and myocardium or individual blood vessels. Covered approaches include a new technique for the heart ventricles segmentation based on dynamic contrast-enhanced CT images and automatic vessel segmentation techniques. We also include a section that explains a mesh generation technique for the recovered geometries. These meshes are used later in the book to solve numerically the systems of partial differential equations governing the deformation of elastic tissues and the dynamics of blood flow. Mathematical models describing these phenomena are introduced in Chapter 4. The model of blood flow dynamics in the heart and vessels includes the Navier−Stokes equations posed in time-dependent domains. These equations as well as equations governing the motion of deformable elastic medium are derived from basic conservation laws. We next introduce the fluid−structure interaction problem that describes the coupled dynamics of the blood flow and elastic walls of the vessels. For each of the models, the chapter discusses basic mathematical properties required for understanding their performance in cardiovascular applications. Discretization techniques and algorithms to solve these models numerically are the subject of Chapter 5. Besides providing details of the computational techniques and examples of generic and patient-specific simulations, the chapter includes all necessary background information about the finite element method for fluids and elasticity as well as a concise review of the numerical linear algebra algorithms used to solve systems of discretized equations.

Real-time patient-specific simulations are often based on models of reduced complexity. If only basic (averaged) blood flow characteristics are required, then a common approach is to apply spatial reduction techniques. Chapter 6 introduces, classifies, and compares so-called lumped parameter or 0D models of the cardiovascular system. This is the most simplified but still useful modeling approach, where the region of interest (whole organism or its local part) is virtually represented by a set of interconnected compartments. The chapter goes into details of two most popular lumped parameter approaches that explore electrical analogies and mechanical modeling. Numerical integration procedure for finding approximate solutions to these models is considered. Furthermore, the chapter discusses

how to make such reduced models to account for certain cardiovascular pathologies. Chapter 7 extends our discussion of reduced models to the simulation of blood flow in large networks of vessels. In such setting, vessels are represented by edges connecting junction nodes and altogether forming a graph. Spatial averaging of the full fluid−structure interaction model leads to a system of 1D hyperbolic equations for averaged blood flow characteristics, posed on the graph. The exposition of the chapter includes the derivation of the system with boundary and junction conditions. Through accounting for all necessary assumptions, we emphasize certain limitations of 1D reduced flow models and consider the numerical procedure to solve the system of ordinary differential equations on the graph. We then proceed with the geometric multiscale modeling, where models of varying spatial dimensions are coupled together for the purpose of the better *local* resolution of the blood flow. Two last sections of the chapter are devoted to the discussion of how different physiological conditions may be incorporated in such reduced models. This includes different mechanical properties of the vessel's walls, valves, nonhomogenous surrounding tissues, external forces depending on body position and physical load, and also a number of common pathological conditions.

Chapter 8 discusses mathematical models of blood circulation and nutrition transport in normal and angiogenic capillary networks. The development of new microvessels, i.e., angiogenesis, is a vital process for wound healing, embryonic development and growth of muscle or adipose tissue. It also plays a fundamental role in the growth of a malignant tumor, which is accompanied by intense reorganization of a microcirculatory network. The structure of microcirculatory networks is complex with extremely high density of microvessels, thus requiring special models for its description. The chapter starts with reconstruction algorithms of the microcirculatory network structure and continues with microcirculatory flow models. Since it is not feasible to resolve flow details in individual capillary vessels, the models operate with statistical characteristics of the blood flow. The remainder of the chapter is devoted to coupling of microcirculation and tumor growth models.

Chapter 9 addresses several clinical applications of regional patient-specific hemodynamic models. The applications include stenting of leg arteries, coronary arteries, and cerebral arteries. We introduce the notion of fractional flow reserve, an important characteristic for the evaluation of stenosed coronary arteries, and discuss its use in the predictive patient-specific numerical modeling. The book proceeds with applications of cardiovascular models to optimize protocols of antitumor therapy in Chapter 10. In this chapter, the microcirculatory and tumor growth models are coupled with the models of nutrition supply and drug administration. The cumulative model is then applied to predict efficiency and to optimize protocols for the combined antitumor chemo- and antiangiogenic therapy.

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A large part of the work presented here was done within the research group in simulation of blood flow and vascular pathologies at the Institute of Numerical Mathematics of the Russian Academy of Sciences. We acknowledge the support of the group by the Russian Science Foundation through the project 14-31-00024 “Multiscale modeling of hemodynamics for patient-specific medical treatments in cardiology, vascular neurology, and oncology”. The Institute of Personalized Medicine at Sechenov University provided a venue for interdisciplinary collaboration. We thank the University for administrative support.

CHAPTER 2

Basic facts about human cardiovascular system

2.1 Introduction

The cardiovascular system consists of three main parts: the heart, the vessels, and the blood. These components work together for maintaining living conditions of the body. The heart periodically contracts and pumps the blood through the network of vessels. The vascular network is divided into systemic and pulmonary loops. These two circuits are connected into one closed loop by the heart through its chambers. Each loop has arterial and venous parts. Arterial parts start from the heart ventricles and ramify in the organs and tissues throughout the whole organism. They end up with capillary network. In the venous parts, the capillaries merge into venules, and further into veins and, finally, converge to the vena cava and pulmonary vein, which are joined with the heart auricles (atria).

The following physiological phenomena drive the blood flow through the body: the blood ejection from the heart due to the contraction of its chambers, the peristaltic pumping of blood in the microcirculation, the skeletal−muscle pump, the respiratory pump, and the heart sucking effect. In short, the blood is ejected from the ventricles, and then it goes subsequently through the arterial and venous parts and returns to the heart auricles. In the systemic loop, the blood flows through the organs and tissues. It delivers oxygen, glucose, and other nutrients. In the pulmonary loop, the blood flows through the lungs. It delivers carbon dioxide to the alveoli and gets a new portion of oxygen.

The fraction of blood in an average adult human organism is approximately 6%−8% of the body weight. The two principal types of the components of the blood are plasma and cells suspended in the plasma (formed elements). Plasma is a water solution of low-molecular organic and inorganic substances. Formed elements are classified as red blood cells (RBCs or erythrocytes), white blood cells (WBCs or leukocytes), and platelets (thrombocytes) (see Fig. 2.1). The essential hemodynamical property of the blood is its viscosity. The viscosity strongly depends on the volume fraction of the RBCs (hematocrit), which is about 40%−45% in the normal case.

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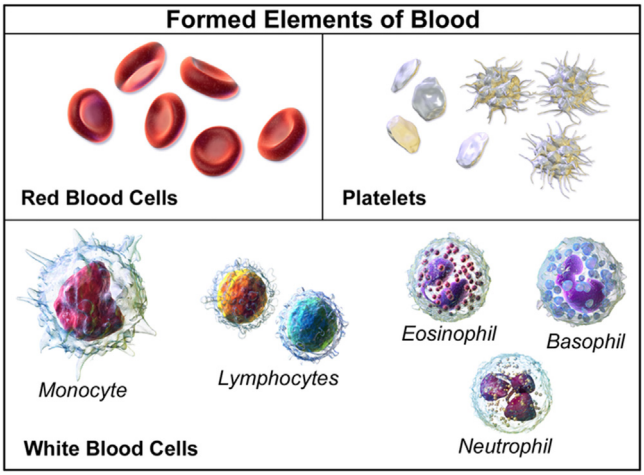

Figure 2.1
The formed elements of the blood. *Source: Blausen.com staff (2014). Medical gallery of Blausen Medical 2014. WikiJournal of Medicine 1 (2). http://doi.org/10.15347/wjm/2014.010.*

The primary functions of the blood are nutrients supply (oxygen, glucose, acid fats, amino fats, etc.); metabolic wastes transport to the lungs and kidneys (carbon dioxide, sulfates, phosphates, etc.); other transport (hydrogen ions, hormones, immunoglobulins, drugs, etc.); temperature, and *pH* regulation. Some blood components participate in inflammatory processes: WBCs fight infections, and platelets initiate blood coagulation and clot formation. Almost all oxygen and carbon dioxide are transferred by blood in the bounded state with the RBCs. All other substances are dissolved in plasma.

2.2 Heart as a pump

The heart pumping is the main factor, which enables the blood flow through the whole vascular network. Electric, mechanical, and hydrodynamic mechanisms are responsible for the successful heart functioning. First, the sinoatrial node produces the electrical impulse (action potential). Next, the impulse is transmitted by the electrical conduction system of the heart, which includes bundle of His, bundle branches, fascial branches, and Purkinje fibers (see Fig. 2.3). Further, auricles contract during His bundle and bundle branches excitation, while ventricles contract during Purkinje fibers excitation after a short delay followed by auricles contraction. Finally, the blood is ejected to the aorta and pulmonary artery (see Fig. 2.2, 2.3). This is a complex hydrodynamical process, which is determined by the anatomical features of the ventricles: unidirectional valves, complex shape, trabecules, and complex movement of the ventricular walls. The myocardium perfusion and nutrients supply is performed by a portion of blood, which is directed from the aortic root to the coronary circulation.

2.2.1 Anatomy

The principal scheme of the heart is shown in Fig. 2.2. For our modeling purposes, we can think of the heart as a set of two successive pumps, which are also called left and right heart. The pumps are combined together by vascular network. Each pump consists of two successive chambers: auricle and ventricle. The ventricles are larger and thicker than atria and can produce larger stress. The auricles are separated from the ventricles by the unidirectional atrioventricular valves. The left ventricle is separated from the aorta by the unidirectional aortic valve. The right ventricle is separated from the pulmonary artery by the unidirectional pulmonary valve. Thus, the blood flow through the heart is unidirectional. The right ventricle receives the blood from the right auricle and pumps it to the pulmonary circuit. The left ventricle receives the blood from the left auricle and pumps it to the systemic circuit.

All chambers walls have the same material structure. The heart wall is divided into three layers: endocardium, myocardium, and epicardium. Endocardium is a small thin layer of endothelial cells, which is the lining inner surface of the chambers. Endocardium of the ventricles has trabecules, which are rounded or irregular muscular columns. The trabecules protrude from the inner surface of the right and left ventricle of the heart and prevent suction. Myocardium is composed of cardiac muscle fibers (cardiomyocytes), which

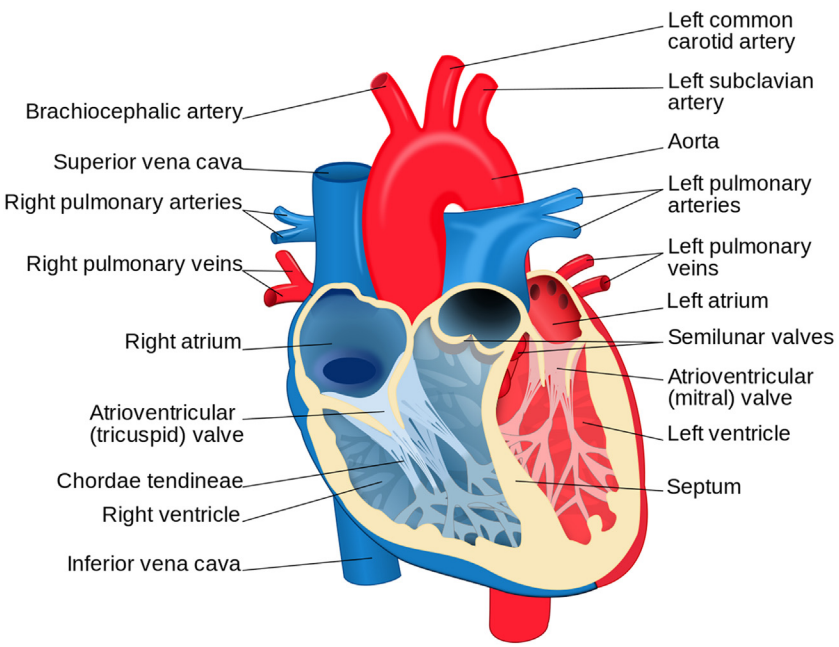

Figure 2.2

The heart. *Source: ZooFari, available at https://commons.wikimedia.org/wiki/File:Heart_diagram-en.svg.*

enable heart contractions. Cardiomyocytes are connected to each other by gap junctions. They are organized in fibers, which in turn are organized in sheets. The sheets are separated by cleavage planes. The fiber and sheet orientation varies throughout the ventricles. At any small segment of myocardium, there always exist some fibers, which respond to the stress in any direction. The structure of the atria and ventricular orientation has been recently studied by 3D diffusion tensor magnetic resonance imaging [7,8].

The outer layer of the heart is epicardium. It consists of a thin layer of connective tissue and fat. Pericardium is the thick, membranous sac, which surrounds the heart. Together with endocardium, it protects and lubricates the heart with the pericardial fluid. It helps to reduce friction between pericardial membranes.

2.2.2 Electrical activity

Cardiomyocytes are the muscle fibers that form the chambers walls of the heart. They are spatially organized for optimal adenosine triphosphate (ATP) and calcium delivery to sarcomeric myosin and ionic pumps during every excitation-contraction cycle. The 3D structure of the human left ventricular myocyte has been recently studied in Ref. [9]. Interactions of actin and myosin filaments are responsible for the cell contraction, which is regulated by the electrical activity of the cell through the cellular membrane permeability. There is interconnection of the membrane potential and membrane permeability to some small inorganic ions: permeability varies during the heart cycle due to the change of the potential difference across the membrane, whereas the potential difference depends on the relative permeability to the ions. This complex interplay of coupled physiological processes is often addressed by numerical simulations [10–15].

The fluid inside the heart cells contains mainly potassium (K^+) ions together with some amount of sodium (Na^+), chlorine (Cl^-), and calcium (Ca^{2+}) ions. The extracellular fluid contains mostly Na^+ and Cl^- ions with some amount of K^+ ions. The depolarization and repolarization of the cell membrane during an action potential is driven by the flow of current carried by Na^+, Ca^{2+}, and K^+ ions. The steep upstroke in the beginning of the action potential results from the rapid opening of Na^+ channels following a stimulus and the consequent inward flow of Na^+ ions, which depolarizes the membrane. It is followed by a smaller inward current of Ca^{2+} ions. It balances an outward current of K^+ ions and maintains the plateau of the action potential. Finally, the outward current carried by K^+ ions becomes significant, which causes repolarization of the membrane and returns it to the initial resting state.

The principal scheme of the conducting system of the heart is shown in Fig. 2.3. The sinoatrial node (SA node) spontaneously generates electrical impulse (action potential), which initiates myocardium excitation and, thus, cardiac cycle. The rate of the impulses is

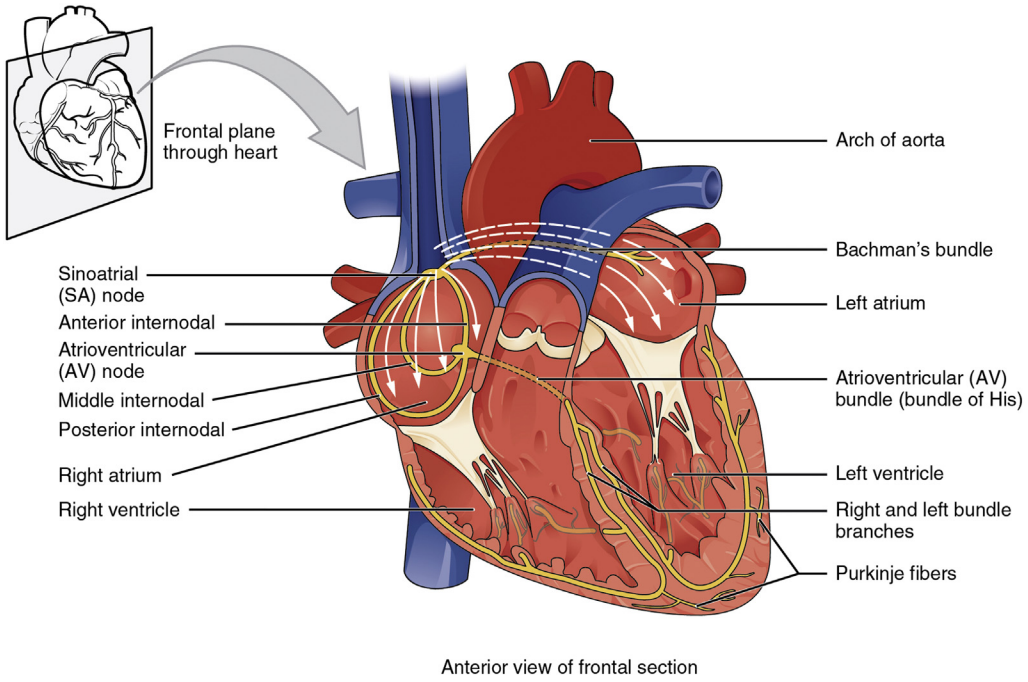

Figure 2.3

Conducting system of the heart. *Source: OpenStax, Anatomy and Physiology. OpenStax CNX. Available at http://cnx.org/content/col11496/.*

controlled by the nerves. The SA node is located in the myocardial wall near the junction of sinus venarum and right atrium. Electrical signals arising in the SA node causes auricles contraction. Then, they travel to the atrioventricular node (AV node), which is located between the auricles and the ventricles. The action potential is conducted through the left and right His bundles to the appropriate Purkinje fibers on each side of the ventricles, which causes ventricular contractions [16].

An action potential is conducted along the muscle fibers at a speed that depends on the diameter of the fiber, its branching, and electric current available to depolarize the next section of the fiber represented by a cardiomyocite. The fiber and fiber sheet orientation also cause substantial effect to the propagation of the action potential. It propagates two to three times faster along the fibers, than across it within the sheet. The speed of action potential propagation orthogonal to sheets is two to three times slower than orthogonal to fibers within the sheets.

Electrical impulses from the SA node propagate through all tissues in the body and attenuate with the distance from the SA node. The electrical activity of the heart can be recorded by the electrodes placed on the surface of the thorax. This process is called electrocardiography (ECG). Computational simulations of ECG help to reveal the features

of impulse propagation from the SA node and provide new insights to the diagnostic of arrhythmia and other heart diseases [17,18].

2.2.3 Myocardial perfusion, ischemia, and infarction

The blood supply of the myocardium is maintained by the coronary arteries, which are mostly located in epicardium. Coronary blood flow is well autoregulated. It remains stable in a wide range of perfusion pressure. Therefore, it maintains sufficient myocardium supply with nutrients.

Ischemia is insufficient tissue supply with oxygen and other nutrients. Infarction is the tissue necrosis due to the prolonged ischemia. Myocardial ischemia is characterized by an unbalanced myocardial oxygen supply and demand. It leads to the loss of myocardial contractility, changes in the membrane potential, ventricular fibrillation, and complete heart block. Irreversible damage includes ATP decrease, stop of anaerobic glycolysis, *pH* and lactate increase, high level of osmolality, membrane damage, cellular and mitochondrial swelling, amorphous densities in the mitochondria, etc. [19]. These changes are the reasons for cardiac dysfunction, arrhythmias, myocardial infarction, and a sudden death.

The usual mechanism for the development of acute myocardial infarction is the rupture or erosion of a vulnerable atherosclerotic coronary plaque with the subsequent totally occluding thrombus. The other possible scenarios are partial occlusion or occlusion in the presence of collateral circulation. Acute myocardial infarction is classified into six types [20].

Microvascular dysfunction in patients with hypercholesterolemia, hypertension, and diabetes mellitus may be a reason for abnormal myocardial perfusion even in the absence of epicardial coronary artery disease (CAD) [21]. Microvascular dysfunction is related to the endothelial function abnormality, which causes autoregulatory mechanisms disorder.

Typically, the overture to the obstructive CAD is a long-term process. Patients are often asymptomatic for decades. Then, the process rapidly develops in less than an hour. The ischemia duration is an important factor of its severity. Ischemia duration less than 40 min results in reversible cellular and functional alterations. Ischemia lasting for more than 40 min often leads to the progressive functional loss and irreversible damage [19]. Ischemic tissue indicates the following pathological abnormalities: loss of oxidative phosphorylation, accumulation of the toxic compounds due to anaerobic metabolism, and acidosis resulted from catabolic reaction [19].

Thus, urgent reperfusion of coronary flow must be provided for the patients with acute myocardial infarction. The invasive treatments such as stenting, angioplasty, thrombolysis,

and coronary bypass may be applied. The no-reflow phenomenon may be observed in the patients with coronary microvascular dysfunction. Therefore, both epicardial coronary flow and microvascular perfusion should be considered and restored [21].

A range of noninvasive testing tools have been developed for clinical evaluation of coronary flow and perfusion, which provide the benefits of increased comfort and less pain. They include single-photon emission computerized tomography, myocardial contrast echocardiography, positron emission tomography (PET), stress cardiovascular magnetic resonance imaging, and cardiac computed tomography. Noninvasive cardiac imaging plays an important role in the diagnosis of coronary artery disease and in the decision-making for surgical interventions [22].

2.3 Large vessels

The heart supplies blood with the energy. The vessels conduct the blood through all parts of the organism. The vessels carrying blood from the heart ventricles to the microcirculation are called arteries, and the vessels carrying blood from the microcirculation to the auricles are called veins. At first glance, vessels are just elastic tubes. However, they have many additional features. Vascular wall may contain different amount of elastin fibers, collagen fibers, and muscle cells. The vascular wall may be affected by the regulatory and autoregulatory mechanisms, muscles, sphincters, and chemicals. Some vessels have a system of unidirectional valves.

2.3.1 Vascular network anatomy

There are two loops, which are formed by the vessels (see Fig. 2.4). In the systemic loop the aorta starts upward from the left ventricle, and then it turns to the 180° and goes downward. Two coronary arteries are started immediately form the aortic root. They supply the heart. There are three branches coming from the aortic arch: brachiocephalic artery, left common carotid artery, and left subclavian artery. These arteries supply the head and upper extremities. The descending part of the aorta is divided into thoracic and abdominal parts. The radius of the descending aorta decreases with the distance from the heart. The thoracic aorta supplies the lung's muscles and other tissues of the thoracic region. The abdominal aorta supplies the organs and tissues of the abdominal cavity (stomach, kidneys, liver, etc.). The abdominal aorta is divided into two common iliac arteries, which supply the lower extremities.

The structure of veins is similar to that of arteries. The average radius of the arteries and veins decreases with the distance from the heart. However, the total cross section of the vessels increases with the distance from the heart. Approximately 80% of the total blood volume is located in the systemic circulation. Veins contain approximately 80% of the

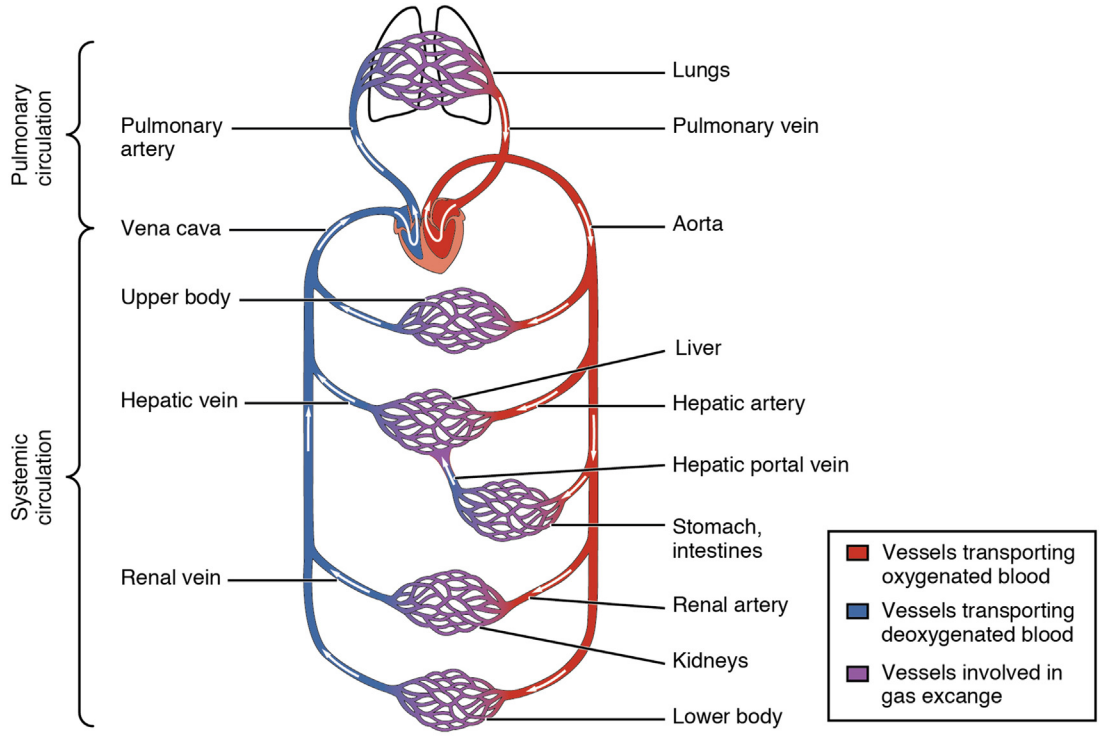

Figure 2.4
The scheme of the cardiovascular system. *Source: OpenStax, Anatomy and Physiology. OpenStax CNX. Available at http://cnx.org/content/col11496/.*

total blood volume. Systemic arteries and veins are organized into networks due to numerous anastomoses. Pulmonary arteries and veins are organized into trees.

2.3.2 Vascular wall structure, elasticity, viscoelasticity

The vessel walls can change their cross-sectional shape and area in response to the applied stresses, e.g., by transmural pressure. Elastic properties and thickness of the vessel depend on its proximity to the heart and on its function. The elasticity is determined by the structure and composition of the vascular wall. Regulatory mechanisms also affect vascular elasticity (see Section 2.3.3).

The walls of all large vessels in the human body are structurally decomposed into three layers: intima, media, and adventitia (see Fig. 2.5).

Intima and adventitia are much thinner than media. Intima is primarily composed of a layer of endothelial cells lining the vessel wall. Adventitia primarily consists of fibroblasts, fibrocytes, and bundles of collagen fibers. Medium is composed of elastic membranes, collagen fibers, and smooth muscle cells. The relative ratio of these three components in