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Anatomy, Mechanical Properties, and Biomechanics

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ISBN 978-3-030-14817-1 ISBN 978-3-030-14819-5 (eBook)
https://doi.org/10.1007/978-3-030-14819-5

Library of Congress Control Number: 2019936004

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Coronary artery disease (CAD) can cause inadequate myocardial perfusion and poor contractility, resulting in deficient cardiac output and potential heart failure. CAD is the leading cause of death worldwide, and by 2020, it is estimated that CAD will be the leading cause of disease burden (e.g., direct and indirect financial cost, disability, mortality, morbidity) worldwide. In the United States, specifically, CAD places the most severe clinical and financial burden of the healthcare system than any other disease conditions. Currently, over 16 million Americans have CAD, which is the leading cause of cardiovascular death in the United States (one out of every six deaths is caused by CAD). CAD is closely related to other conditions such as obesity, diabetes mellitus, hypertension, and heart failure. As a result, treatment for CAD in the United States leads to the highest cost of any disease condition (~ $100B per year). Between 2010 and 2030, the total direct medical cost of cardiovascular diseases is projected to triple, from $270 billion in 2010 to $800B in 2030.

The coronary circulation consists of an integrated system of complex anatomy, mechanical properties, boundary conditions representing the hemodynamics, and myocardial-vessel interaction, which leads to phasic patterns of coronary blood flow into, within, and out of the myocardium. Coronary blood flow is substantially heterogeneous spatially (throughout the myocardium) and temporally (within cardiac cycle). These temporal and spatial heterogeneities are important physiologically and clinically but are difficult to study at the inner layers of the myocardium, where susceptibility to ischemia is an important clinical phenomenon. Hence, rigorous validated models of the coronary vasculature, mechanical properties, boundary conditions, and myocardial-vessel interaction are critical to produce realistic predictions of blood flow throughout the wall of the heart.

The biomechanics of coronary circulation is intimately related to the blood supply of the heart (globally) as well as to the initiation of and progression of CAD (locally). Hence, there is a significant need for understanding coronary blood flow in both health and disease at the global and local level. This book is intended to address this need by providing a comprehensive compendium on coronary circulation both *globally*, as it relates to blood perfusion of the heart muscle, and *locally* at the site of CAD initiation and progression. Furthermore, this is the first text to provide a distributive analysis of coronary circulation based on detailed measured vasculature and mechanical properties. This book provides quantitative physiology of the coronary circulation, using biomechanics to couple structure with function. It provides a detailed biomechanical synthesis of coronary circulation based on a distributive analysis of measured properties of the system (anatomy, mechanical properties, and boundary conditions) that addresses both the global and local circulations.

This book, ***Coronary Circulation: Anatomy, Mechanical Properties, and Biomechanics***, provides a quantitative description of the coronary vasculature and mechanical properties. A number of boundary value problems are solved to provide analyses of coronary blood flow and stress distribution through the coronary vasculature, e.g., longitudinal pressure and flow distribution, local bifurcation flow and stress analysis, etc. The book consists of the following chapters: (1) Biomechanics, (2) Morphometry of Coronary Vasculature, (3) Mechanical Properties and Microstructure of Coronary Arteries, (4) Constitutive Models of Coronary Arteries, (5) Network Analysis of Coronary Circulation: Steady-State Flow, (6) Network Analysis of Coronary Circulation: Pulsatile Flow, (7) Scaling Laws of Coronary Vasculature, and (8) Local Coronary Flow and Stress Distribution.

Chapter 1 provides an overview of the basic principles of biomechanics including terminology, approach, conservation laws, and some numerical methods of solutions. It sets the framework for the biomechanical approach to understand the function of an organ (specifically the heart) in a quantitative manner. Chapter 2 focuses on the anatomy and morphometry of the coronary vasculature. It provides both the reductionist (reducing the system into its individual components) and integrationist (rebuilding the system from the individual components) approaches to understand the coronary vasculature. Chapter 3 uses the reductionist approach to understand the material properties of the coronary vasculature; i.e., it provides the mechanical response (or stress-strain relation) of individual segments of the coronary vasculature. It also provides the microstructural vessel wall data that dictates the macrostructural response of the vessels to loading. Chapter 4 uses the integrationist approach to synthesize the constitutive relation of the vessel wall. Both phenomenological and microstructural constitutive laws are discussed. These mechanical measurements and mathematical formulations connect microstructure (e.g., elastin, collagen, ground substance, cells) to macro-mechanics (e.g., response to mechanical load such as pressure, axial load, torsion). Chapters 5 (steady-state flow) and 6 (pulsatile flow) present network analysis of global circulation (pressure-flow relation, perfusion, etc.) including models of coronary flow regulation. Analysis of coronary circulation is presented that includes the interaction between myocardial contraction and coronary blood flow. Chapter 7 presents scaling laws that explain the design of the coronary vasculature. The principles of biomechanics are used to connect form (e.g., geometry of vasculature including diameters, lengths, numbers) with function (e.g., blood volume, flow). Finally, Chapter 8 presents local blood flow mechanics and the resulting vessel wall stresses (e.g., shear stresses, intramural stresses). These analyses provide the mechanical culprits for the spatial propensity of CAD initiation and progression.

Biomechanics-based modelling, which couples form (i.e., the structure of coronary vessels) with function (i.e., coronary perfusion), is the major theme of this book. The mathematical models of coronary circulation are both informed and calibrated by experimental data to minimize **ad hoc** assumptions. The predictions of pressure, flow, shear stresses, and intramural stresses, among others, are also validated against experimental data to provide confidence in the models for understanding coronary physiology and pathology. In order to understand local flow patterns, the key equations representing conservation of mass, momentum, and energy are described and applied in the context of the coronary circulatory system as a whole, as well as regionally. The technical details (including morphometric and mechanical data as well as mathematical analysis) are summarized in appendices for the interested reader to avoid technical detraction from the main discussions. The distributive models of the coronary vasculature presented are based on actual measured anatomy and mechanical properties of the system as opposed to the "black box" approach of lumped models. These idealized lumped models lack the real anatomy or mechanical properties of the system (i.e., analog circuits that do not reflect the actual distributed vasculature or its material properties).

This book is intended for bioengineers, physiologists, cardiologists, surgeons, and industry engineers who desire a clear understanding of coronary blood flow for further research, diagnostics, and therapeutics. Although a balanced treatment of the topic is attempted with numerous references to other works, there is an emphasis on the work conducted by my research team over the past 25 years. My hope is that this work can embrace and stimulate the next generation of scientists, bioengineers, researchers, and clinicians to continue to contribute to this very vital area of research to understand the coronary circulation and heart function. Moreover, a similar biomechanical approach may be used by researchers to formulate a similarly detailed systematic understanding of other organs and body systems.

This work would not have been possible without the dedications and tireless efforts of numerous talented students, fellows, and collaborators over the past 25 years. The coauthors, listed on my publications in the reference section, are my collaborators to whom I am greatly indebted. The knowledge presented in this book would not have been possible without their tireless efforts. I would also like to acknowledge my current team for their dedication and contributions (in alphabetical order): Henry Chen, Huan Chen, Susy Choy, Bill Combs, Ali Dabiri, Yaghoub Dabiri, Greg Dick, Fred Field, Lijuan Fu, Xiaomei Guo, Ling Han, Terry Hubbard, Carlos Labarrere, Xiao Lu, Bhavesh Patel, Mengjun Wang, and Yanmin Wang. A special thanks to Prof. Dhanjoo Ghista and Dr. Amy Spilkin for the review and critique of the chapters and Martha Sanchez for technical assistance. Finally, I would like to thank Merry Stuber of Springer for her constant encouragement and commitment to this project and Maria David for shepherding this book to publication.

This book is dedicated to the memories of my father (Sleewa Kassab, 1934–1967) who passed away young when I was a toddler. I hope to inspire my children (Gabriel and Gianno) as my father's memories and courage have inspired me.

San Diego, CA, USA Ghassan S. Kassab

Contents

Chapter 1
Biomechanics

1.1 Introduction

There is no doubt that one of the most significant health problems facing people around the world is vascular disease that compromises perfusion of vital organs (e.g., heart, brain, etc.). Abnormal mechanical stresses and deformation of blood vessels have been identified as key culprits in the initiation and progression of vascular disease. To understand the blood circulation through blood vessels, one must consider the blood, the blood vessel wall, the tissue surrounding the vessel wall, the geometry of the vascular system, and the driving forces from pumping of the heart. Blood vessels are remarkable organs that nurture organisms, transport many enzymes and hormones, contain blood cells that flow or clot when needed, and transport oxygen and carbon dioxide between the lungs and the cells of the tissues. Physiologists study these important functions of the vasculature as they relate to the functioning of the body. Bioengineers apply engineering principles to understand biological systems. For the bioengineer, the understanding of the biomechanics of circulation is a central focus to explain vascular health and disease.

The coronary vasculature is a complex system of millions of elastic vessel segments of hierarchical sizes, branching patterns, branching angles; and internal and external loading conditions within the heart muscle. A rigorous biomechanical analysis of coronary blood flow throughout the heart muscle requires a complete quantitative description of the 3D architecture of the coronary blood vessels, detailed knowledge of the mechanical properties of the coronary blood vessel wall, blood rheology, hemodynamic boundary conditions, and conservation laws (Fig. 1.1). Such biomechanical analysis is necessary for understanding the mechanisms of mechanical interactions between the contracting heart and the embedded elastic coronary vasculature as the dynamics of deep myocardial wall vessels cannot be studied experimentally at the required spatial and temporal resolution.

Stress and strain are fundamental concepts in understanding biomechanics of coronary vasculature. Stress is related to force per area and arises from contraction of

G. S. Kassab, *Coronary Circulation*, https://doi.org/10.1007/978-3-030-14819-5_1

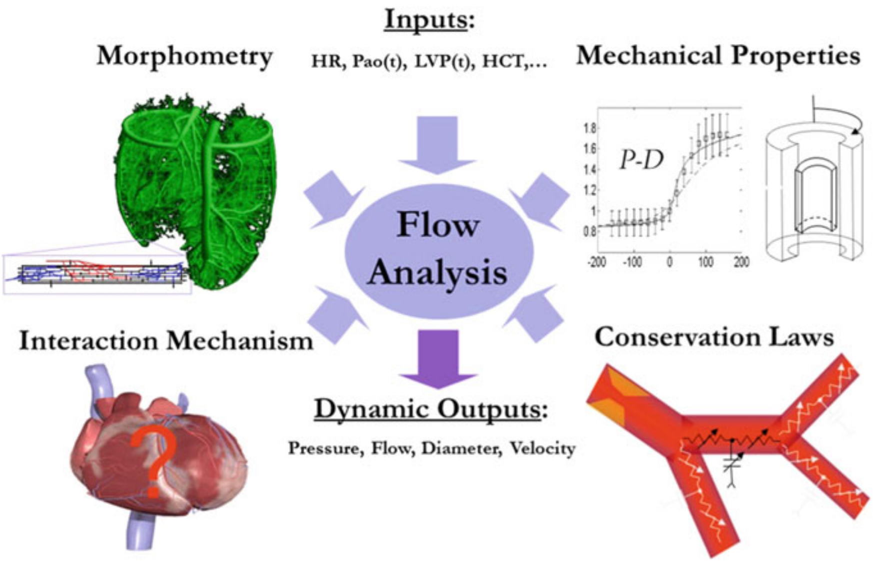

Fig. 1.1 Schematic of the various components of the coronary circulation including morphometry of the coronary vasculature (microcirculatory unit is shown in the left panel stemming from the full vasculature model), pressure–diameter (P-D) relation that describes the mechanical properties of vessels, blood rheology (*HCT* hematocrit; apparent viscosity, etc.), boundary conditions (*Pao* aortic pressure, *LVP* left ventricular pressure, *HR* heart rate, etc.), conservations laws (mass and momentum) to yield the dynamic pressure, flow, diameter, and velocity distributions as a result of the coronary vessel–myocardial interaction especially in the deep layers of the heart which are not easily amenable to direct experimental observations (denoted by "?"). Courtesy of Dr. Ravi Namani

heart muscle which leads to loading forces on blood vessels such as blood pressure and flow. Since the blood pressure and flow are applied loads, they must be resisted or opposed by internal stresses generated in the vessel wall to maintain equilibrium of forces. Strain refers to the amount of stretch or deformation the blood vessel undergoes due to the applied loads (pressure and flow). Although strain can be measured in vivo using several medical imaging techniques such as ultrasound, X-ray, and MRI, there is no instrumentation for in vivo measurement of stresses. Biomechanics provides a means for determining the stresses and strains in blood vessels.

Biomechanics is broadly defined as mechanics applied to biology. Mechanics constitutes the study of stresses and deformations in structures and motion of bodies, while biology is the study of life (both within and around us). Hence, biomechanics is the interface of these two large fields, which includes the study of the coronary circulation, as well as such areas as gait analysis, rehabilitation, sports performance, flight of birds, motion of sperm, birth labor, surgical and interventional devices, biomaterials, plant and animal growth and remodeling, stresses in the heart wall and limbs, prosthesis design, and invertebrate mechanics, to name just a few.

Continuum mechanics is the study of internal reaction of an object to external forces. External forces may consist of body forces such as gravitational and electromagnetic or surface forces such as normal and shear. The axioms of continuum mechanics consist of the following: (1) Newton's laws of physics, (2) Laws of thermodynamics, (3) Continuum remains a continuum, (4) Existence of stress and strain, and (5) Stress is a unique function of strain and strain rate. Continuum mechanics is concerned with the mechanical behavior of fluids and solids on a continuum scale, such that the physical properties of fluids and solids (e.g., material properties, mass, density, momentum, energy) can be defined by continuous functions. In the continuum model, the scale of interest is large as compared with the characteristic dimension of the discrete constituents, e.g., tissues in an organ, cells in a tissue, proteins in a cell. The key concepts of continuum mechanics are stress (force/area), strain (a dimensional change) and rate-of-deformation (strain rate). The physical laws of continuum mechanics include the stress and strain relationship in terms of the material properties, conservation of mass, momentum, and energy. The material properties of a continuum are mathematically described by the constitutive equation that relates stress to strain and strain rate. The constitutive equation provides information on the material properties or constitution of the tissue. For a simple spring, the constitute equation relates force to displacement through the spring constant (stiffness). Biological tissues are differentiated from inanimate objects through their unique constitutive equations which change in space (i.e., heterogenous composition) and time (i.e., grow, age, and remodel) in a living organism.

Physiology is the study of the normal function of living systems (Singer, 1959). The physiologist generally seeks to understand the relationship between structure and function of physiological systems, ranging from the cardiovascular system to pulmonary system, renal system to urological system, neurological to endocrine system, and orthopedic to spinal system. Biomechanics provides the physical and analytical tools to connect structure and function, with the major objective of understanding problems in physiology with mathematical accuracy. In the context of vascular mechanics, the major objective of biomechanics is to accurately determine the blood flow in the vessels, which is the major determinant of molecular, cellular, tissue, and vessel homeostasis.

The relationship of form and function or the structure–function relation is one of the oldest axioms in biology and medicine and it has been of great interest to many investigators in many different organs (e.g., heart, brain, liver, kidney). One premise of the structure–function relation is the notion of homeostasis and the major impetus in biomechanics is motivated by the need to understand function and physiology and subsequently patho-physiology. Biomechanics is the link between structure and function, i.e., biomechanics uses structure along with laws of mechanics, and initial and boundary conditions to deduce function.

Biomechanics is very relevant to vascular disease because the propensity of the most common vascular disease (i.e., atherosclerosis) is not random but has predilection to certain regions of the vascular system (DeBakey, Lawrie, & Glaeser, 1985). DeBakey and colleagues examined over 13,000 patients and classified five major categories of atherosclerosis including category I for the coronary arteries as

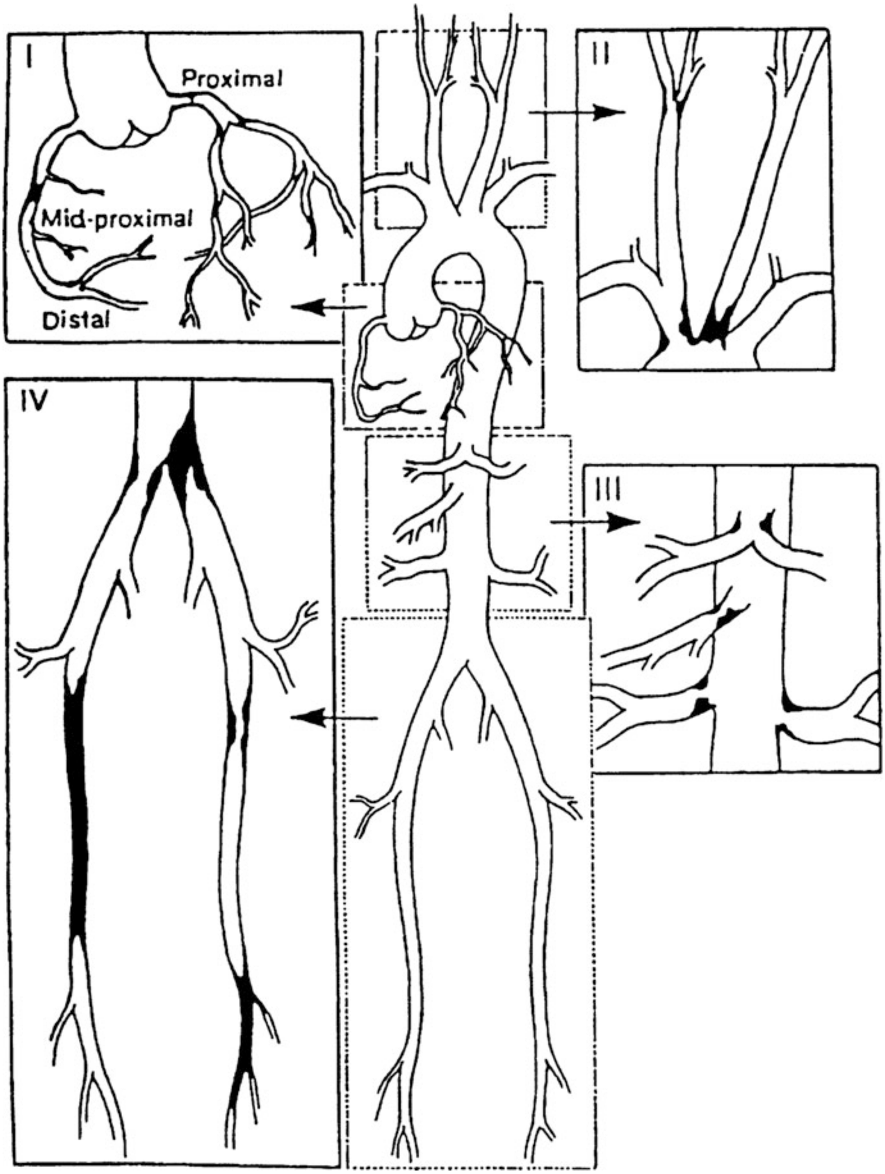

Fig. 1.2 Schematic of distribution of atherosclerosis in the vascular system including coronary arteries in category I (left upper panel). Reproduced from DeBakey et al. (1985) with permission

shown in Fig. 1.2. The various categories include regions of bifurcations, curvature, and infra-renal regions. The common biomechanical characteristics of these regions include transient flow reversal (i.e., flow disturbances, low fluid shear, oscillatory shear index) and high intramural stresses at regions of curvature. Biomechanics is necessary to understand these phenomena and to devise therapies to mitigate and treat atherosclerosis.

This chapter outlines a basic biomechanical approach for the understanding of coronary vascular physiology and pathology. The geometry, material properties, and boundary conditions in conjunction with the laws of mechanics allows a precise and quantitative description of the problem, and associated method of solution (e.g., by employing the finite element method, computational fluid dynamics method, and fluid–solid interaction method). We shall describe each of the components of this approach, which will set the stage for the study of specific problems of the coronary circulation in the subsequent chapters.

1.2 Basic Terminology in Biomechanics

Table 1.1 summarizes some common terminology used in biomechanics. The concept of stress and strain is intimately related to force and deformation. Forces applied to fluids cause flow, while forces applied to solids cause strain or deformation (i.e., solids resist the stresses). When external forces are applied to a vessel, it deforms to resist the forces. It is common to use distensibility and stiffness to describe the deformation and the resistance to deformation, respectively. Definition of these parameters for the blood vessels can be difficult since no single parameter can describe the complex mechanical behavior of the blood vessels. To arrive at useful approximations typically used in physiology, it is important to understand the basic relations between stresses (i.e., force) and strains (i.e., deformation).

1.2.1 Stress

Stress is force per unit cross-sectional area (Table 1.1 and Fig. 1.3), i.e., force per unit area of the material on the positive side (exterior) of a vector perpendicular to the surface exerts on the negative side (interior). On any surface, the force may be applied either perpendicular to the surface, such as the bolus pressure (normal stress) exerted on the wall from the blood pressure or from the surrounding tissue (e.g., myocardium), or parallel to the surface, such as the force exerted by the fluid flow (shear stress) on the wall. Normal stresses may be either compressive (e.g., forces on coronary vessels from surrounding heart muscle) or tensile (e.g., forces on heart wall from blood pressure). A force may be applied in any direction and can induce stresses and strains in various directions.

At any given point in the body, the state of stress is described by a stress tensor which consists of three normal stresses and six shear stresses (three are independent). Tensors are geometric objects that are used as the language of continuum mechanics. Both stress and strain are tensor quantities represented by a 3×3 matrix with nine components in three-dimensional (3D) space (2×2 in 2D). Since both stress and

Table 1.1 Common biomechanics terms

Term	Definition
Stress	Force per unit surface area that the part lying on the positive side of a surface element (the side on the positive side of the outer normal) exerts on the part lying on the negative side. Stress is a tensor quantity with six independent components. Three of the components are called normal stresses, and the remaining three components are called shear stresses. A normal stress is perpendicular to the surface while a shear stress is parallel to the surface. Figure 1.3 shows an example of stresses induced in vessel wall in response to pressures and flow
Strain	Force applied to a solid causes deformation or strain. Consider a string with initial length L_o and stretched length L. Strain is useful to describe the change in length by dimensionless ratios such as L/L_o or $(L - L_o)/L_o$ as this eliminates the absolute length from consideration. Elongation causes tensile (positive) strain while shortening causes compressive (negative) strain. Figure 1.4 shows an example of strains induced in vessel wall in response to pressure and axial force
Elastic modulus	Proportionality constant between stress and strain in given direction. For example, Hooke's law applies for a homogenous, isotropic, linearly elastic material implying that in a given dimension a single elastic modulus describes the stiffness, i.e., spring constant k. The mechanical behavior in soft biological tissues is generally nonlinear and the elastic modulus is not constant but depends on the load
Isotropy	Materials whose mechanical properties do not depend on directions are said to be isotropic. Biological tissues are usually anisotropic, mainly due to their heterogeneous, layered structure
Viscoelasticity	Time dependence of the response to stress or strain. Stress relaxation, creep, and hysteresis are features of viscoelasticity
Preconditioning	In mechanical testing of living tissues in vitro, the loading and unloading processes are repeated for a number of cycles until the stress–strain relation becomes stabilized and repeatable results are obtained
Constitutive equation	A constitutive equation describes the material properties of a material; e.g., the stress–strain relation. A simple example for a spring is the equation of the form $F = kx$, where F is the force or stress and x is the displacement or strain and k is the material constant
Zero-stress state	Tissue configuration where no stress is present. For a tubular organ, the zero-stress state is obtained by making radial cuts in a ring of tissue such that it springs open into a sector. The difference in strain between the zero-stress state and the no-load state where all external forces are absent is called residual strain
Plastic deformation	Deformation that does not return to its initial state when the stress is removed

strain are symmetric tensors in the absence of external moments, the number of independent components reduces to six in 3D (i.e., only three unique shear components). The rows correspond to the direction of outer normal to a surface, whereas the columns correspond to the direction of force (Fung, 1994).

In a cylindrical tube (e.g., a blood vessel), radial, circumferential, and longitudinal components of stress can be defined in the respective directions. These are the

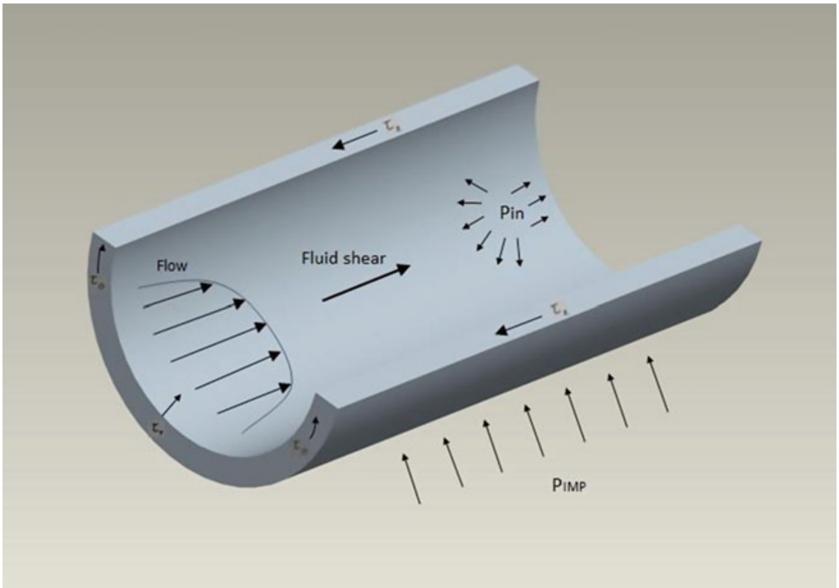

Fig. 1.3 Schematic of blood vessel under pressure, flow, and external (e.g., intramyocardial pressure, IMP for the heart) loadings. The isotropic pressures act in all direction to induce circumferential (τ_θ), axial (τ_z), and radial (τ_r) stresses. The blood flow induces shear stress on the endothelium

normal components of stress in the wall of the cylinder (Fig. 1.3). There are also three additional shear components. In tubular organs, the major tensile stress induced by distension is in the circumferential direction (Dobrin, 1978). During luminal pressure loading, the equilibrium condition requires the force in the vessel wall in the circumferential direction to be balanced by the force in the vessel lumen contributed by the inflation pressure. Under the assumption that the vessel geometry is cylindrical, it can be shown that the average circumferential wall stress is $\sigma = Pr/h$, where P, r, and h are the pressure, internal radius, and wall thickness, respectively. This formula is commonly known as Laplace's law (see Appendix 1 for derivation) which is applicable for thin wall vessels, such as blood vessels. This equation explains clinical phenomenon such as why aneurysms will continue to expand once dilated, and why rupture occurs when segments are excessively distended, i.e., as the radius increases, the stress or tension increases which leads to further increase in radius and so on until the failure stress is reached. Another important implication of this equation is that the wall stress is related to pressure and the radius-to-wall thickness ratio. It should be noted that the stress is averaged over the thickness of the segment and does not describe the transmural distribution of stress across the wall thickness, as in the case of a thick-walled vessel, i.e., a thick-walled cylinder will bear the highest tensile stress on the inner surface. Furthermore, residual strain (i.e., strain that remains in the tissue when all external loads are removed) is often found in biological tissues as shown by a vessel segment opening

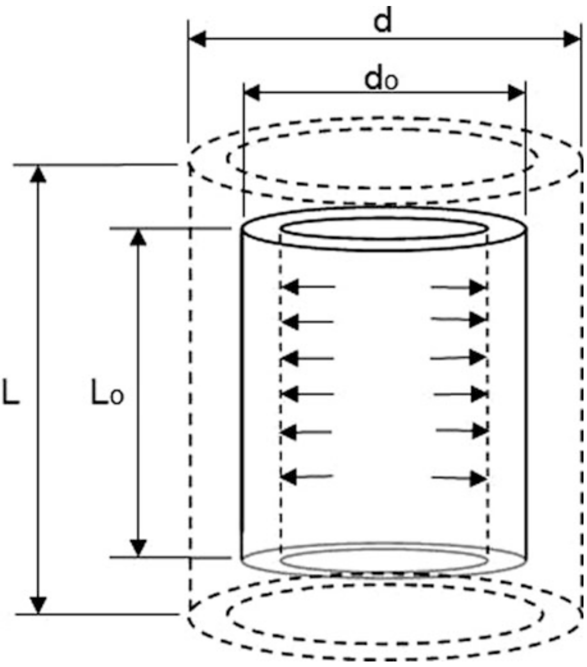

Fig. 1.4 Schematic of definition of strain in the circumferential (pressurized) and axial (elongated) directions. The circumferential deformation can be defined as the stretch ratio d/d_o or strain $(d - d_o)/d_o$ (Lagrangian if in reference to undeformed configuration) or $(d - d_o)/d$ (Eulerian if in reference to deformed configuration), etc. Similarly, the axial stretch can be defined as L/L_o or $(L - L_o)/L_o$ or $(L - L_o)/L$, etc.

into a sector when cut radially (Chap. 3), which is not considered in Laplace's equation.

1.2.2 Strain

Strain refers to stretch or deformation of a material and is usually expressed as a fraction of the initial length (Lagrangian strain, ε), as defined in Table 1.1 (see Fig. 1.4 for vessel as an example). It may also be defined in terms of a stretch ratio, λ (length divided by initial length referred to as Lagrangian), which is useful if the material is incompressible since the product of the stretch ratios in the three principal directions (i.e., circumferential, axial, and radial) is equal to 1. Hence, if the stretch ratios in two directions are known, the third stretch ratio can be computed. The relation between Lagrangian strain (ε) and stretch ratio (λ) is $\varepsilon = \lambda - 1$. Alternatively, strain can be defined in reference to deformed state referred to as Eulerian. In contrast to stress, strain (Lagrangian or Eulerian) is dimensionless and the gradient in circumferential strain is more uniform across the wall in tubular organs. The dimensionless property of strain facilitates the comparison of various experiments. The strain is dependent on the determination of the correct initial length which may be uncertain since in blood vessels and other biological tissues (e.g., smooth muscle cells of bladder), the resting length can accommodate a broad range of physiology.