

Chapter 4

Biomechanics of Blood Vessels: Structure, Mechanics, and Adaptation

Takeo Matsumoto, Shukei Sugita, and Toshiyuki Yaguchi

Abstract Basics and recent advances in blood vessel wall biomechanics are overviewed. The structure of blood vessel walls is first introduced with special reference to heterogeneity in the mechanical properties of artery walls at a microscopic level. Then basic characteristics of the mechanical properties of blood vessel walls are explained from the viewpoints of mechanical parameters used in clinical investigations, elastic and viscoelastic analysis, and effects of smooth muscle contraction. As examples of mechanical analysis of blood vessel walls, stress and strain analyses of artery walls as thin- and thick-walled cylinders, analyses considering residual stress and microscopic heterogeneity, are introduced. One of the most important topics in the blood vessel mechanics, mechanical responses and adaptations of blood vessel walls, is then discussed from the viewpoints of long- and short-term responses of artery walls to increases in blood pressure or flow. And finally, the importance of studying microscopic mechanical environment to elucidate these mechanical adaptations is pointed out.

Keywords Artery • Vein • Biomechanics • Smooth muscle • Endothelium • Elastin • Collagen • Intima • Media • Adventitia

4.1 Structure and Function of Blood Vessel

The blood vessels are the network of tubing that transports blood throughout the body. Blood delivers substances necessary to the body such as oxygen and nutrients to the tissues and removes carbon dioxide and metabolic waste products from the tissues. There are three major types of blood vessels: the arteries carrying the blood away from the heart, the capillaries that enable the exchange of chemicals and water

T. Matsumoto (✉) • S. Sugita • T. Yaguchi
Department of Mechanical Engineering, Nagoya Institute of Technology,
Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan
e-mail: takeo@nitech.ac.jp

between the tissues and the blood, and the veins carrying blood from the capillaries back toward the heart. Among them, mechanical properties of arteries larger than a few millimeters in diameter have been studied extensively for their ease in handling and their importance in clinical medicine. In this chapter, we mainly focus on larger arteries.

The arteries and veins have three layers: tunica intima, tunica media, and tunica adventitia, or simply intima, media, and adventitia. The intima is the thinnest layer with the thickness around 10 μm . It is a single layer of endothelial cells aligning in the direction of blood flow on a thin layer of elastic tissue called the internal elastic lamina. It plays important roles relating to vascular diseases, especially to atherosclerosis, including prevention of thrombus formation, control of permeability to various substances, and blood flow sensing and control of vascular diameter (see Sects. 4.4.1 and 4.4.3 for details). The media is the thickest layer in the arteries and plays major roles in their mechanical properties. It consists of circularly arranged vascular smooth muscle cells, elastic fiber (elastin), connective tissue (mainly collagen), and polysaccharide substances. Smooth muscle cells are a type of muscle cells, and they contract and relax in response to chemical and mechanical stimuli to control the caliber of the vessel. Elastin is one of the most elastic materials in biological tissues. Collagen is the main structural protein of the connective tissues and is stiff compared to elastin as shown in the next paragraph. There are two types of arteries, elastic and muscular. The elastic arteries are large arteries close to the heart such as the aorta and the carotid arteries and are abundant in elastin. Their media is made of concentric layers whose unit is called a lamellar unit [1], a pair of elastic lamina mainly made of elastin and a smooth muscle-rich layer (Fig. 4.1). The muscular arteries are less abundant in elastin, and their media has a rather homogeneous structure (Fig. 4.2). The media and the adventitia are separated by another thin elastic tissue called external elastic lamina. The adventitia is the thickest layer in the veins. It is entirely made of collagen fibers and fibroblasts that synthesize collagen. Capillaries consist of little more than a layer of endothelium and occasional connective tissue.

From the viewpoint of biomaterials, blood vessel wall can be viewed as a composite material consisting of components with various mechanical properties such as elastin, collagen, and smooth muscle cells. Elastin is highly elastic material with Young's modulus of ~ 500 kPa [2–4]. It remains elastic at least until its length is doubled (Fig. 4.3). Compared to elastin, collagen is highly stiff material with Young's modulus of ~ 1 GPa (Fig. 4.4) [5, 6]. Although collagen fibers can bear high stress in the body, they are less deformable and become fractured at relatively low strain (less than 10 %). In case of artery wall, they align obliquely to stretch direction and are corrugated in a physiological state. Such oblique alignment and corrugation allow the artery walls large deformation (~ 100 %) in the physiological condition as well as their strain-hardening properties (see Sect. 4.2.1.1 for details). In contrast to elastin and collagen that behave mostly linearly elastic materials, smooth muscle cells are highly viscoelastic. Their mechanical properties change drastically depending on their contractile state. Their Young's modulus ranges from 10 kPa under relaxation to 100 kPa under contraction (Fig. 4.5) [7]. Smooth muscle cells

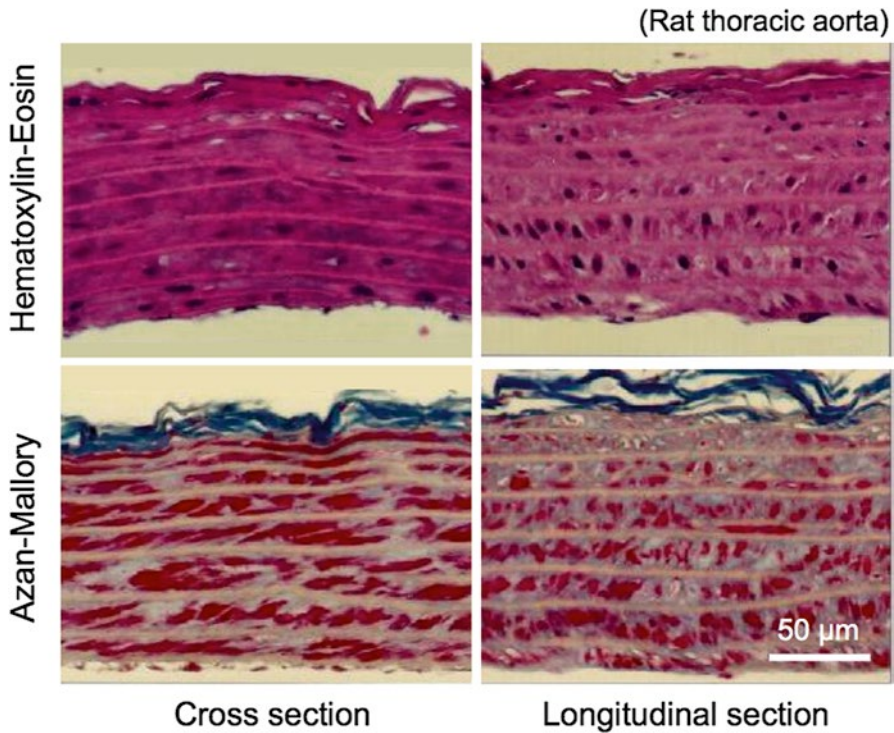


Fig. 4.1 Histological sections of an elastic artery fixed in a physiological condition, stained with hematoxylin-eosin (nucleus, *purple*) and Azan-Mallory (smooth muscle, *red*; collagen, *blue*; unstained, elastin)

also have a unique characteristic, *i.e.*, mechanical adaptation. They change their dimensions and mechanical properties in response to mechanical stimulation they receive to maintain homeostasis of intramural mechanical environment (see Sect. 4.4.2 for details).

The mechanical properties of the vascular wall are determined by relative amount of these components, their alignment, and their slackness, etc. The aorta, an elastic artery, is abundant in elastin and the largest artery. Due to its abundance in elastin and its large size, the aorta is the most compliant vessel in the vascular system. It expands in response to blood pressure increase in systole to store a part of the blood pumped out from the heart and thus helps to decrease the systolic pressure, *i.e.*, the load of the heart. In diastole, it shrinks in response to pressure decrease to maintain distal blood flow just like an air-pressurized reservoir in a water gun (Windkessel effect). As one goes from proximal to distal side, the diameter and wall thickness of the artery decrease monotonously, and the relative amount of smooth muscle cells and the ratio of collagen to elastin increase. Because collagen is much stiffer than elastin, distal arteries are generally stiffer than the proximal arteries. The collagen to elastin ratio continues to increase in the veins. The veins have larger diameter and

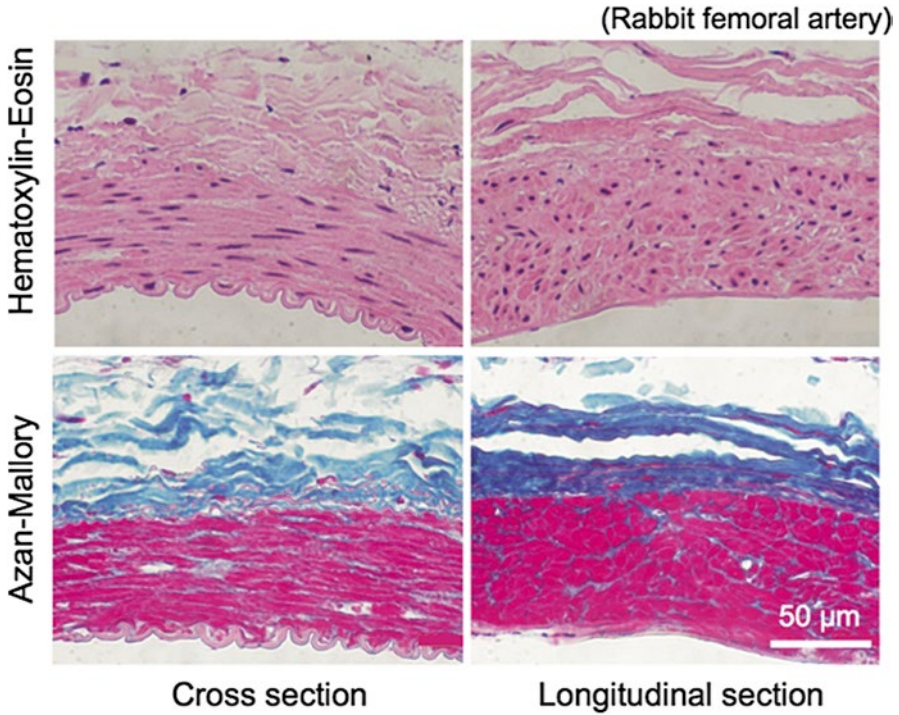


Fig. 4.2 Histological sections of a muscular artery fixed in a physiological condition, stained with hematoxylin-eosin (nucleus, *purple*) and Azan-Mallory (smooth muscle, *red*; collagen, *blue*; unstained, elastin)

Fig. 4.3 Stress-strain relationship of an elastic lamina (porcine thoracic aorta). Nominal stress-strain curve is almost linear until nominal strain exceeds 1.0, *i.e.*, until the length is doubled

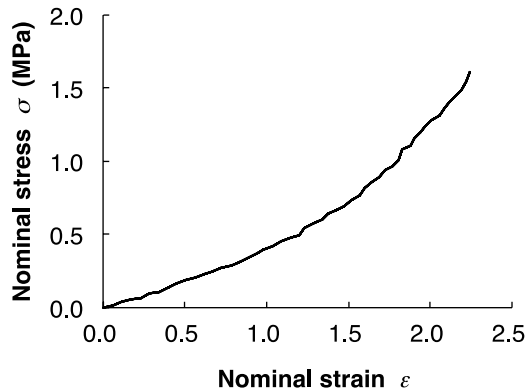


Fig. 4.4 Stress-strain relationship of a rabbit patellar tendon (Redrawn from [6])

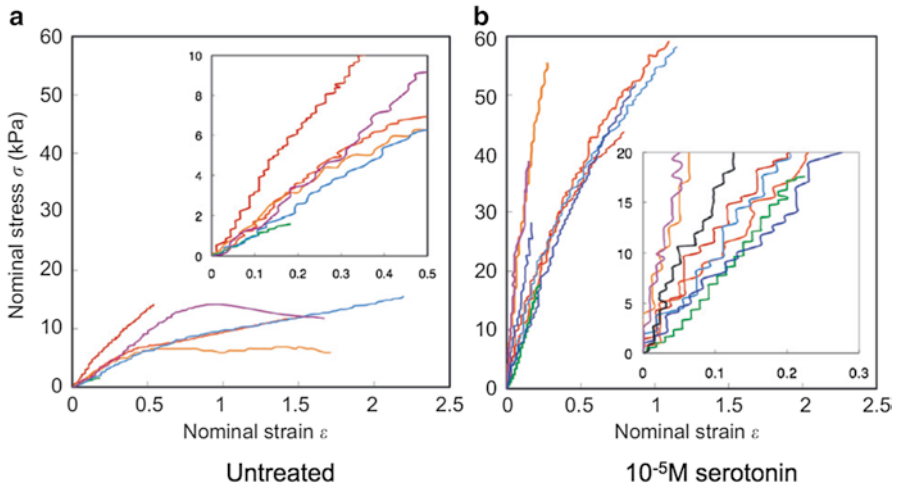
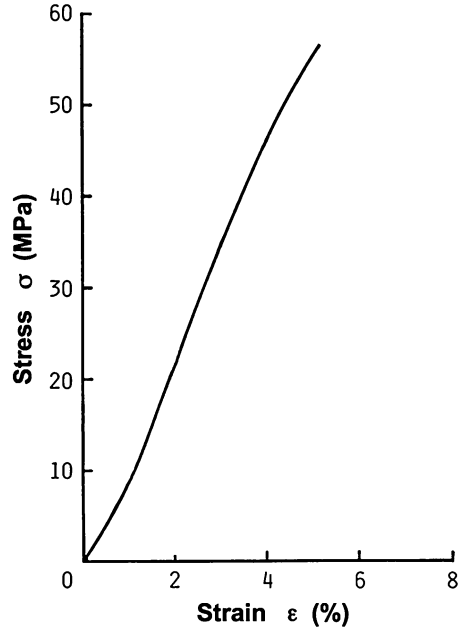


Fig. 4.5 Tension-elongation relationship of vascular smooth muscle cells obtained from rabbit thoracic aorta. Smooth muscle contraction was induced with serotonin (Reprinted from Ref. [7], Copyright 2012, with permission from Elsevier)

thinner wall compared to arteries at the same anatomical position. Because they occupy about 3/4 of the total vessel volume and show large deformation in the physiological condition, the veins serve as a reservoir of the blood that controls the circulating blood volume and called a capacitance vessel. Veins in the extremities have valves to prevent regurgitation. Blood vessel network from the arterioles to venules via capillaries is called a microcirculatory system. The microcirculatory system is called a resistance vessel for it is the major part of resistance in the circulatory system. The arterioles with abundant smooth muscle cells are responsible for the maintenance of the blood pressure by changing their diameter by smooth muscle contraction and relaxation.

4.2 Mechanics of Blood Vessel

4.2.1 Basic Characteristics

Blood vessel walls are exposed to various mechanical stresses in vivo. In case of artery wall, its intraluminal surface is subjected to mean pressure of ~ 13.3 kPa (100 mmHg) and pulse pressure of ~ 5.3 kPa (40 mmHg). Arterial walls are stretched by 30–50 % in the longitudinal direction, which can be confirmed by arterial contraction in the longitudinal direction after excision. Wall shear stress of a few Pa is applied to the intraluminal surface due to the blood flow, and wall shear stress oscillates during the cardiac cycle. Due to these mechanical stresses, the artery diameter changes by ~ 10 % and its length changes by a few % during the cardiac cycle. Twisting of the vessel is very small [8].

In case of the veins, quasistatic pressure of ~ 1.3 kPa is applied to the walls. The intraluminal pressure sometimes has a negative value due to the pressure difference between veins and the heart and/or due to other physical forces from the surrounding tissues. Under these circumstances, outer radius of the veins can change by several tens of percent.

From the mechanical point of view, keywords expressing basic characteristics of the blood vessel walls are as follows: (1) large deformation and nonlinear mechanical properties, (2) incompressibility, (3) viscoelasticity, and (4) anisotropy. Details of each characteristic are described in the following sections.

4.2.1.1 Large Deformation and Nonlinear Mechanical Properties

The vascular walls undergo large deformation, and its physiological strain ranges from several tens of percent to 100 %. Mechanical properties such as elasticity depend on the magnitude of pressure applied to the vessel walls significantly. Arterial wall shows remarkable strain-hardening properties. It is quite deformable in subphysiological pressure range, while in suprphysiological pressure range, it becomes less deformable sharply as pressure increases. This means that we need to

Table 4.1 Pressure dependence of incremental elastic modulus of the rabbit thoracic aortas

Pressure (mmHg)	Incremental elastic modulus (kPa)
20	200 ± 20
50	200 ± 10
100	430 ± 30
125	1,550 ± 150
150	4,480 ± 360
180	8,200 ± 720

Mean ± SEM, $n = 16$

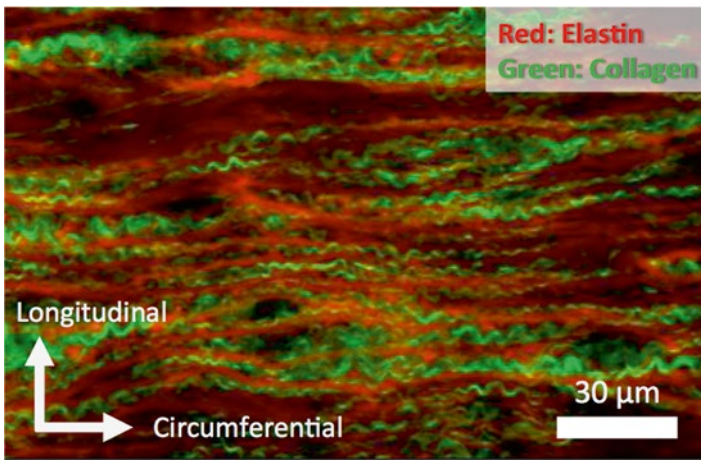


Fig. 4.6 Corrugation of collagen fibers in a rabbit thoracic aorta pressure-fixed at 80 mmHg

pay attention to strain or pressure levels when comparing elastic moduli between blood vessels. For example, in rabbit thoracic aortas, when pressure increases from 2.7 kPa (20 mmHg) to 23.9 kPa (180 mmHg), their circumferential stretch ratio increases from 1.1 to 2.0, and an incremental elastic modulus E_{inc} (see Sect. 4.2.2 for details) increases from 200 kPa to 8,200 kPa by 40 times (Table 4.1).

Nonlinearity of the stress-strain relationship of blood vessels can be explained by the degree of undulation and variation of alignment of collagen fibers in the vessel walls. Both elastic and collagen fibers in the fiber direction have linear mechanical properties. As described in Sect. 4.1, Young's modulus of elastin is ~ 0.5 MPa and that of collagen fibers is ~ 1 GPa. In low-pressure region, collagen fibers remain wavy (Fig. 4.6) and align obliquely to the circumferential direction [9], while elastic fibers are straight, and thus, the incremental elastic modulus is low (Table 4.1). In high-pressure region, stiff collagen fibers become straight and begin to be stretched [10], resulting in the strain hardening of the blood vessel wall. Since collagen fibers are not stretched in low-pressure region, breaking strain of the aorta ($\sim 100\%$) is in

the range between breaking strain of elastin (~200 %) [2] and that of collagen (~10 %) [5]. The strain-hardening property of the blood vessel is very important for the arteries to prevent vessel rupture (see Sect. 4.3.1 for details).

4.2.1.2 Incompressibility

Generally speaking, soft biological tissues are mainly composed of water. For example, water content of canine arterial walls is around 70 % of total volume [11]. Because water is incompressible, *i.e.*, does not change its volume during deformation, the artery wall is also considered to be incompressible. Carew et al [12] measured the volumetric change of dog thoracic aortas during inflation-extension test. They found that volume strain was only 0.06 % when 40 and 70 % of strain were imposed in longitudinal and circumferential direction, respectively.

4.2.1.3 Viscoelasticity

Viscoelastic materials exhibit not only elastic characteristics but also viscous when undergoing deformation. Elastic materials deform when stretched and quickly return to their original state once the stress is removed. Viscous materials deform linearly with time when a stress is applied. Viscoelastic materials have elements of both of these properties and, as such, exhibit time-dependent strain. The effect of viscoelasticity on mechanical properties of large blood vessels is relatively small. Change in the stiffness due to change in strain rate could be several 10 % at most. Therefore, large vessels are often treated as elastic tubes. However, it should be noted that effects of viscoelasticity could be much larger and cannot be ignored in small arteries. For further discussion, see Sect. 4.2.3.

4.2.1.4 Anisotropy

Major constituents of blood vessels such as collagen, elastin, and smooth muscle cells predominantly orient in the circumferential-longitudinal plane. Since mechanical properties of arteries depend on the properties of the individual constituents and their orientations, mechanical properties in the radial direction are different from the circumferential and longitudinal directions. Even in the circumferential-longitudinal plane, anisotropy has been observed. Uniaxial tensile test has shown that the tensile strength of the aortas is larger in the circumferential direction than in the longitudinal direction [13]. In a bulge test, in which a platelike specimen is sandwiched with two plates having a hole at their center and pressurized from one side, porcine thoracic aortas initiated cracks in the circumferential direction [14]. Pressure-imposed tests for tubular specimens have indicated that the difference in an elastic modulus is at most twofolds for large arteries [15]. However, because

most of the blood vessels are tethered in the longitudinal direction and their compliance is mostly determined by the deformability in the circumferential direction, the mechanical properties in the circumferential direction, *i.e.*, pressure-diameter relationship, which is important from a practical standpoint.

4.2.2 Parameters Expressing Mechanical Properties of Blood Vessel

To obtain detailed mechanical properties of blood vessels, we excised them from bodies and loaded them with a wide range of pressure to obtain pressure-diameter relationship with an apparatus shown in Fig. 4.7, for example. A quasistatic and dynamic pressure-diameter curve of canine common carotid artery is shown in Fig. 4.8 [16]. The pressure-diameter curve shows characteristics of the nonlinear and downward-convex relationship as described in Sect. 4.2.1. These characteristics are seen in both arteries and veins. It also has a hysteresis as shown in the difference between the loading and unloading limbs. The hysteresis is derived mainly from viscoelasticity of smooth muscle cells. The area of the hysteresis loop depends on the relative volume and the activity of smooth muscle cells.

Stiffness of blood vessels can be measured from the pressure-diameter curve. It is affected by not only Young's modulus but also the geometry of the vessels such as radius and wall thickness. For example, for two cylindrical tubes made of the same material (*i.e.*, with the same Young's modulus) with the same outer radius, one

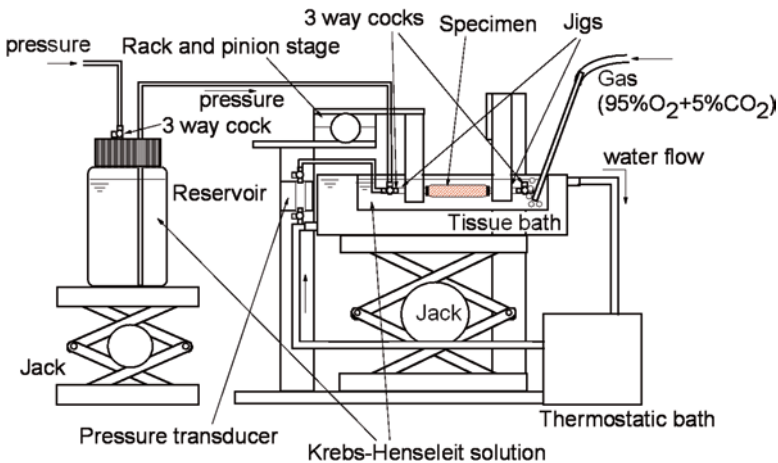
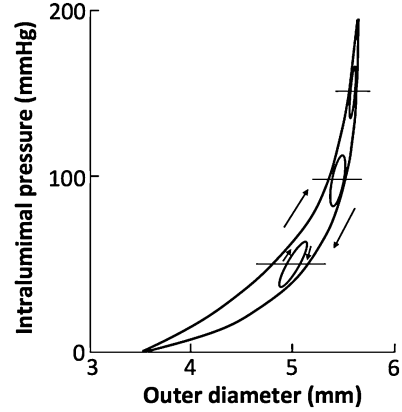


Fig. 4.7 An example of experimental setup for the measurement of pressure-diameter relationship of blood vessels. To mimic physiological condition, specimen was immersed in an aerated Krebs-Henseleit solution at 37 °C and pressurized pneumatically while measuring its outer diameter with a video camera and a video dimension analyzer (not shown)

Fig. 4.8 Pressure-diameter relationship of a canine common carotid artery. The large nonlinear hysteresis loop is obtained in a quasistatic condition, *i.e.*, by changing the intraluminal pressure at the rate of ~ 1 mmHg/s. Small oval loops are obtained in a dynamic condition, *i.e.*, by changing intraluminal pressure sinusoidally at ~ 1 Hz (Reprinted from Ref. [16], with permission from JSME)



with thicker wall is stiffer. Similarly, two tubes made of the same material with the same wall thickness, one with smaller radius is stiffer. Thus, we need to evaluate stiffness and elastic modulus separately.

Although the pressure-diameter curves are highly nonlinear in a wide range of pressure, each of them can be regarded as linear if you divide them into small sections. Then elastic modulus can be defined using a linear equation. When pressure increases from P_i by ΔP_i and outer diameter from D_o by ΔD_o , elastic modulus and stiffness can be calculated from P_i , D_o , and $\Delta D_o/\Delta P_i$. In the following part of this section, some of the representative parameters expressing mechanical properties of the blood vessel are introduced.

4.2.2.1 Incremental Elastic Modulus E_{inc}

The incremental elastic modulus, E_{inc} , which corresponds to Young's modulus of blood vessel wall can be expressed by the following equation [17]:

$$E_{inc} = 1.5 \frac{\Delta P_i}{\Delta D_o} \frac{D_o \cdot D_i^2}{D_o^2 - D_i^2} \quad (4.1)$$

To calculate the incremental elastic modulus, the inner diameter D_i or wall thickness, which is difficult to measure in clinical practices, is needed. This parameter is used mainly in experimental studies for excised specimens, but not for clinical medicine. Usually inner diameter D_i is calculated from inner and outer diameters d_i and d_o , respectively, at no-load state under the assumption of incompressibility of vessel wall as follows:

$$\pi(D_o^2 - D_i^2)\lambda_z / 4 = \pi(d_o^2 - d_i^2) / 4, \quad (4.2)$$

where λ_z is a longitudinal stretch ratio, which is defined as the ratio of the in vivo length of a vessel segment L to its length at no-load state l , *i.e.*, $\lambda_z = L/l$.

4.2.2.2 Pressure Strain Elastic Modulus E_p

The pressure strain elastic modulus, E_p , presenting stiffness of blood vessel can be expressed by the following equation [18]:

$$E_p = \Delta P_i / (\Delta D_o / D_o) \quad (4.3)$$

Since it can be easily calculated from obtained data in clinical practice, it has been used widely not only in experimental studies but also in clinical medicine.

4.2.2.3 Stiffness Parameter β

The stiffness parameter β can be expressed by the following equation:

$$\ln(P / P_s) = \beta(D_o / D_s - 1) \quad (4.4)$$

where P_s and D_s are pressure and outer diameter, respectively, at a reference state in vivo [19]. Normally reference state is taken as $P_s = 100$ mmHg (13.3 kPa). It is well known that pressure-diameter curve of an artery is well fitted by an exponential function. This parameter is obtained based on this knowledge, and the nonlinearity of blood vessels can be eliminated at least partially in the physiological range, *i.e.*, it is relatively insensitive to the variation of blood pressure. And also, this parameter does not require blood vessel wall thickness that is difficult to measure in clinical practices. Thus, the stiffness parameter has been widely used in clinical medicine.

Typical values of these parameters are summarized in Table 4.2 for various species and anatomical sites.

4.2.3 Viscoelastic Properties

It is important to know dynamic mechanical properties of arteries because the arteries in vivo are cyclically stretched during the cardiac cycle. Parameters expressing dynamic mechanical properties can be obtained by measuring the amplitude of the dynamic change in the outer diameter ΔD_o and the amplitude of pressure waveform ΔP_i at various frequencies of the pressure waveform to calculate the parameters shown in Sect. 4.2.2. To investigate the viscoelasticity of arteries in detail, the

Table 4.2 Normal values for parameters expressing elastic properties of blood vessels of various species and anatomical sites [16]

Blood vessel	E_{inc}^a (MPa)	E_p^b (MPa)	β
Thoracic aorta	0.5 (D), 0.9 (R)	0.07 (H)	2.5 (R)
Abdominal aorta	1.0 (D), 2.0 (R)	0.10 (H)	5.6 (H)
Common carotid artery	0.9 (D), 1.5 (R)	0.08 (H)	5.3 (H)
Femoral artery	1.0 (D), 4.0 (R)	0.49 (H)	19.8 (H)
Pulmonary artery	0.6 (D)		
Coronary artery	1.7 (D)		29.8 (R)
Arteriole	0.12 (CM)		
Capillary	0.37 (CM)		
Venule	0.39 (CM)		
Saphenous vein	0.03 (D)		
Jugular vein	1.5 (D)		
Inferior vena cava	0.07 (D)		

D dog, *R* rabbit, *CM* cat mesentery, *H* human

^aIncremental elastic modulus at intraluminal pressure of 100–125 mmHg (13.3–16.6 kPa, from thoracic aorta to capillary) or 10 cm H₂O (1 kPa, veins)

^bAt rest under normal blood pressure

dynamic elastic modulus E_{dyn} and the loss elastic modulus $\eta\omega$ need to be calculated considering phase lag $\Delta\phi$ between diameter and pressure waveform as follows:

$$E_{dyn} = E_{inc} \cdot \cos \Delta\phi \quad (4.5)$$

$$\eta\omega = E_{inc} \cdot \sin \Delta\phi, \quad (4.6)$$

where E_{inc} is the incremental elastic modulus (see Sect. 4.2.2) obtained from $\Delta D_o/\Delta P_i$, η viscosity modulus and ω angular velocity [20]. Figure 4.9 shows an example of dynamic elastic modulus calculated from Eq. 4.5 and normalized with the incremental elastic modulus obtained at static condition. In dynamic conditions, the elastic modulus increases generally by several 10 % from that in a static condition. However, frequency dependency is very low as shown in this figure.

4.2.4 Effects of Smooth Muscle Contraction

Mechanical properties of blood vessels change drastically in response to contractile state of the smooth muscle cells that reside in the media [21]. Smooth muscle cells are a type of muscle cells that exhibit contraction and relaxation in response to various chemical and mechanical stimuli to regulate the diameter of blood vessels. Figure 4.10 shows typical pressure-diameter curves of a canine common carotid artery in which smooth muscle contraction was induced with norepinephrine (NE)

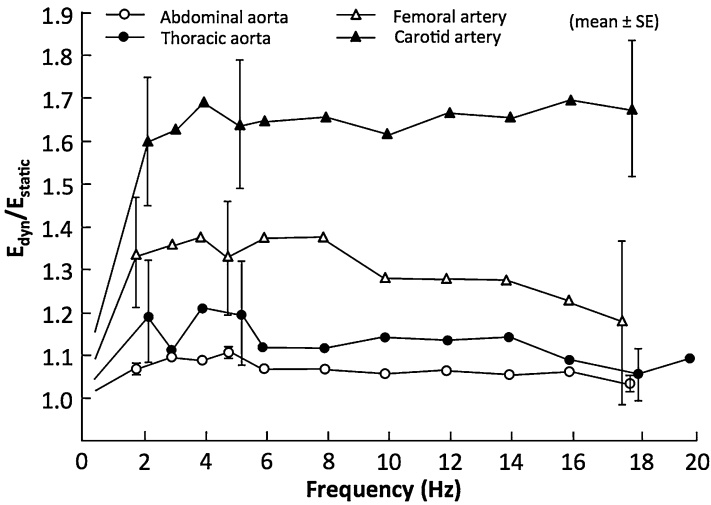
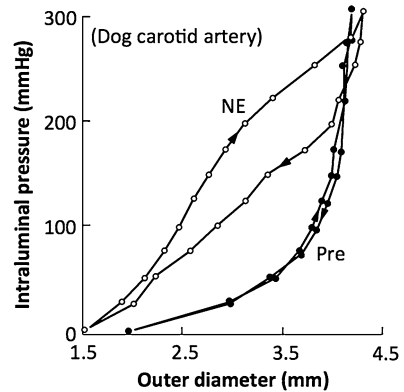


Fig. 4.9 Frequency dependency of dynamic elastic modulus of various arteries obtained from dogs (Redrawn from [20])

Fig. 4.10 Change in mechanical properties of an artery in response to smooth muscle contraction. Pre, before smooth muscle contraction; NE, contraction with 10^{-5} M norepinephrine (Redrawn from [22])



[22]. When norepinephrine is applied, the curve shifts to the left, its shape changes from downward-convex to upward-convex, and the hysteresis loop area increases significantly. External diameters, however, are equal for relaxed and contracted arteries at 300 mmHg. Effects of smooth muscle contraction on elastic properties are complex. Generally speaking, stiffness increases in the region with relatively smaller diameter while it decreases in the larger diameter region. And also, the magnitude of the effects of smooth muscle contraction depends on the relative amount of smooth muscle. The amount of contraction of the diameter in response to smooth muscle activation is 10 % at most for the aorta, while smooth muscle contraction almost occludes the lumen of muscular arteries such as digital arteries.

4.3 Mechanical Analysis of Blood Vessel Walls

Analysis of blood vessel deformation shown in the previous section is important to know the effects of the mechanical properties of the blood vessel wall on the intramural blood flow and pressure. However, we need to know intramural distributions of stress and strain to understand the blood vessel mechanics in detail and to study the mechanism of the mechanical adaptation in the blood vessel wall that will be shown in the next section. In this section, the outline of the various mechanical analyses [23, 24] is reviewed. For the ease of analysis, blood vessels are assumed to be a cylinder with a circular cross section, and the wall materials are assumed to be homogeneous and incompressible. Because most of the arteries are tethered by surrounding tissues in the longitudinal direction and their deformation in this direction is much smaller than the deformation in the circumferential direction, we concentrate on the mechanical analysis in the circumferential direction in this section.

4.3.1 Analysis of a Thin-Walled Cylinder

In reality, blood vessel has a finite wall thickness, and the stress and strain in the inner wall are different from that in the outer wall as shown in the next section. However, if the wall is very thin as in the case of the veins, the difference between the inner and outer walls may be negligible, and analysis on a representative or mean value will be enough. Assumption of thin-walled cylinder can be used not only in veins but also for the arteries with relatively thick wall as long as what you want to know is the mean values of stress and strain and not their radial distributions in the wall.

Mean value of the circumferential stress σ_θ is obtained precisely from the dimensions of blood vessel wall, inner radius R_i and wall thickness H , and intraluminal pressure P_i as follows (Law of Laplace):

$$\sigma_\theta = P_i R_i / H. \quad (4.7)$$

Mean value of circumferential strain can be expressed as extension ratio λ_θ :

$$\lambda_\theta = R_m / r_m = (R_o + R_i) / (r_o + r_i), \quad (4.8)$$

where subscript m indicates mean value, i inner wall, and o outer wall. Lowercase letters indicate reference state, *i.e.*, no-load state, and upper case letters physiological condition. If you assume that the blood vessel wall deforms maintaining its volume, *i.e.*, the wall is incompressible, then the following equation can be obtained:

$$2\pi r_m h = 2\pi R_m H \lambda_z \quad (4.9)$$

and thus

$$\lambda_\theta = R_m / r_m = h / (H \lambda_z). \quad (4.10)$$

As shown in Eq. 4.7, the circumferential stress is proportional not only to P_i but also R_i and inversely proportional to H . If the vessel is pressurized, the increase in σ_θ is much larger than that in P_i because of the increase in R_i and simultaneous decrease in H due to pressure increase. Thus, if the material properties of the wall are linear, the increase in P_i cannot be compensated by the increase in σ_θ over a certain vessel diameter. If this happens in an artery, it will be inflated until burst over a critical pressure. To prevent such a catastrophe, nonlinear (strain-hardening) mechanical properties of the artery are crucial.

4.3.2 Analysis of a Thick-Walled Cylinder

Generally speaking, wall thickness of an artery corresponds to 5–10 % of its radius, and the difference in the mechanical environment between the inner and outer walls cannot be neglected. In such cases, artery wall needs to be analyzed as a thick-walled cylinder to obtain stress and strain distribution in the direction of wall thickness, *i.e.*, radial direction. Strain distribution can be obtained by assuming that the artery wall is consisted of thin-walled cylinder. If it is assumed that a cylinder having the outer radius r_o , inner radius r_i , and length l deforms to a cylinder having the outer radius R_o , inner radius R_i , and length $L = l \cdot \lambda_z$ and that the radius r of a thin-walled cylinder in the unloaded wall becomes R in the deformed state, R can be derived as follows assuming incompressibility:

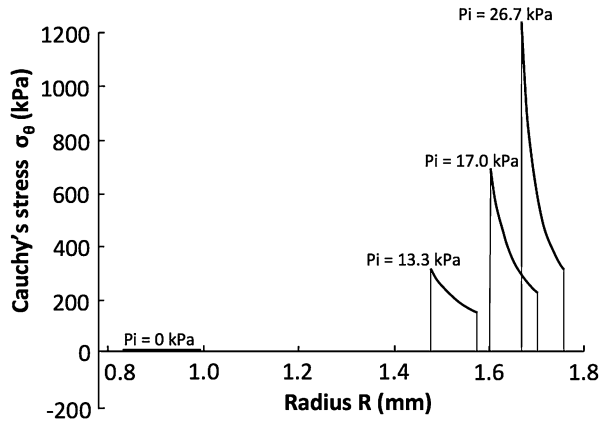
$$R = \sqrt{R_o^2 - (r_o^2 - r^2) / \lambda_z}. \quad (4.11)$$

Circumferential stretch ratio of this cylinder is thus defined as

$$\lambda_\theta(r) = \frac{2\pi R}{2\pi r} = \frac{R}{r} = \frac{\sqrt{R_o^2 - (r_o^2 - r^2) / \lambda_z}}{r}. \quad (4.12)$$

Stress distribution can be obtained assuming that unloaded thick-walled cylinder is in a stress-free state. To obtain stress distribution, we need to know stress-strain relationship of each thin-walled cylinder. The stress-strain relationships can be obtained by assuming a strain energy density function [25]. Pressure-diameter relationship of the artery can be derived by integrating the stress-strain relationships of the thin-walled cylinders. Thus, the strain energy density function can be determined by fitting pressure-diameter curve derived from that function to actual pressure-diameter curve obtained in an experiment (see the literature [25] for details).

Fig. 4.11 Example of stress analysis of a rat thoracic aorta as a thick-walled cylinder (Reprinted from Ref. [25], with permission from ASME)



An example of such stress analysis is shown in Fig. 4.11. High stress concentration appeared in the inner wall with the increase in blood pressure. Generally speaking, when a thick-walled cylinder expands, an increase in the circumferential strain is larger in the inner wall than in the outer. Due to nonlinearity of the stress-strain relationship of the artery, stress increase is exaggerated in high strain region. Thus, sharp stress concentration occurs in the inner wall of the artery.

4.3.3 Consideration of Residual Stress

Does the sharp stress concentration shown in Fig. 4.11 really appear in the artery wall? It looks unnatural to have such stress concentration in a tissue if the rationality and optimality of biological system are considered. One of the reasons for such unnaturalness is that we assume that unloaded thick-walled cylinder is in a stress-free state. Actually, this assumption is not valid in many cases. Figure 4.12 shows an example of shape change of a ringlike specimen obtained from a porcine thoracic aorta upon cutting of the ring. The ringlike specimen sprang open to form an arc upon radial cutting, indicating that there existed compressive residual stress in the inner wall and tensile in the outer before radial cutting. Such residual stress attenuates stress concentration in the inner wall of a thick-walled cylinder (Fig. 4.13). Thus, we need to distinguish the no-load state and the stress-free state.

Figure 4.14 shows the configurations of a vascular wall in three states, stress-free, no-load, and loaded states. The vascular wall was assumed to be thick-walled cylinder in the loaded and no-load states. Inner and outer radii in the no-load state were measured in a ringlike specimen sliced out from a tubular

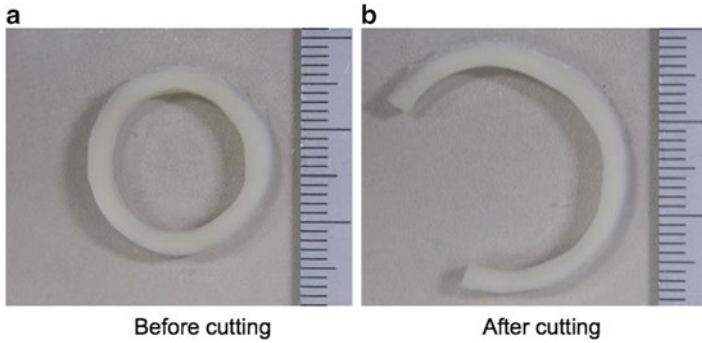


Fig. 4.12 Shape change of a porcine thoracic aorta following radial cutting

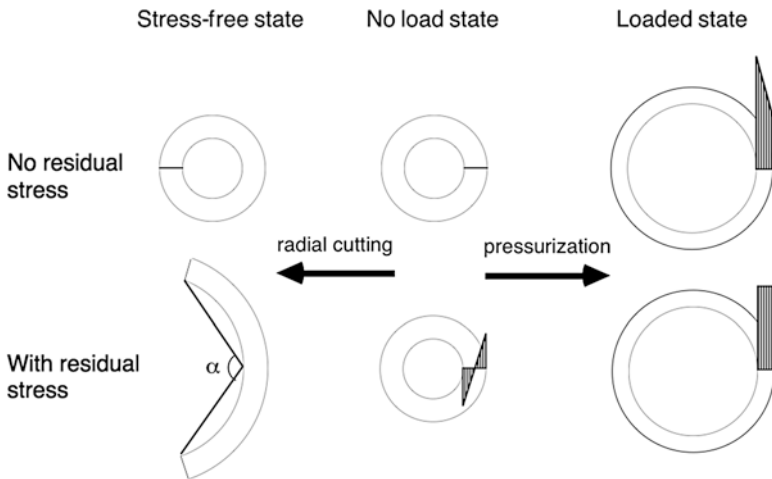


Fig. 4.13 Physiological significance of residual stress in the blood vessel wall. If there is no residual stress in the no-load state, high stress concentration will appear in the inner wall. If stress distribution is uniform in the radial direction, residual stress appears in the no-load state, and this causes opening of the ring following radial cutting

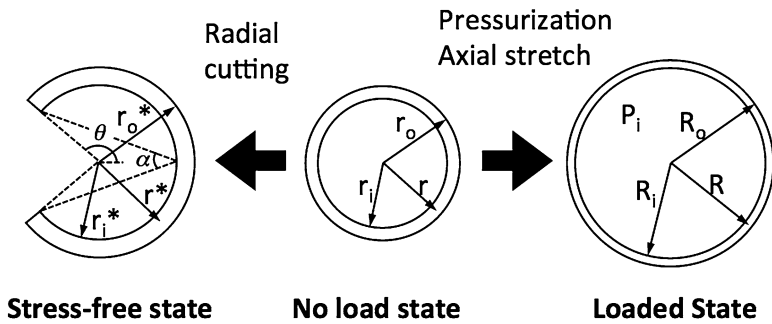


Fig. 4.14 Coordinate system used for strain analysis of a thick-walled cylinder

specimen that had been used to obtain pressure-diameter relationship of the blood vessel. The outer radius in the loaded state was obtained from the pressure-diameter curve, and the inner radius is obtained in Eq. 4.11 in Sect. 4.3.2. The ringlike specimen was then cut radially. If we assume that the aorta is a homogeneous and cylindrically orthotropic tube, the opened-up ring forms an arc of constant curvature and thickness. An opening angle, α , *i.e.*, the angle subtended by the two radii drawn from the midpoint of the arc of the inner wall of the vessel to the inner tips of the arc [26], was measured in the opened-up ring. The effective external radius of the opened-up ring specimen, r_o^* , was then calculated assuming that the mean circumference and the cross-sectional area of the specimen do not change by cutting as follows:

$$r_o^* = \frac{1}{2} \left\{ \frac{\pi}{\theta} (r_o + r_i) + (r_o - r_i) \right\}, \quad (4.13)$$

where θ is one half of the central angle of the arc and is equal to the angle of circumference of the arc, *i.e.*, $\theta = \pi - \alpha$ [25].

Circumferential extension ratio at the radius R in a loaded wall is

$$\lambda_\theta(r) = \frac{\pi R}{\theta r^*}, \quad (4.14)$$

where

$$r^* = \sqrt{r_o^{*2} - \frac{\pi \lambda_z}{\theta} (R_o^2 - R^2)} \quad (\theta > 0), \quad (4.15a)$$

$$= -\sqrt{r_o^{*2} - \frac{\pi \lambda_z}{\theta} (R_o^2 - R^2)} \quad (\theta < 0), \quad (4.15b)$$

or

$$\theta r^* = \frac{\pi}{2} (r_o + r_i) \quad (\theta = 0). \quad (4.15c)$$

An example of radial distributions of circumferential extension ratio is shown in Fig. 4.15. The distributions are obtained from pressure-diameter relationship and the opening angle of rat thoracic aortas in the literature [27]. High stretch ratio appeared in the inner wall as pressure increases when residual strain, *i.e.*, the opening angle, is not considered. Such intraluminal concentration of stretch ratio disappeared when the opening angle is considered. It has been suggested that distribution of circumferential stress is uniform in the radial direction [26–31].

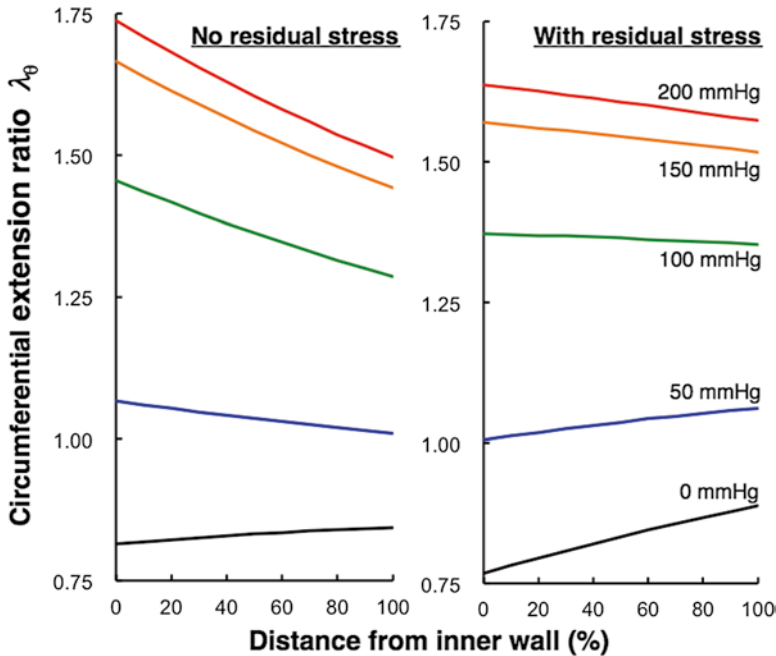


Fig. 4.15 Circumferential strain distribution in the wall of rat thoracic aorta

4.3.4 Consideration of Microscopic Heterogeneity

As stated in Sect. 4.1, blood vessel wall is heterogeneous at a microscopic level. It is composed of materials with various mechanical properties. Such heterogeneity may cause microscopic residual stress. For example, the wall of elastic arteries has layered structure composed of elastic lamina (EL) and a smooth muscle-rich layer (SML) as shown in Fig. 4.1. The EL is composed of elastin whose Young's modulus is ~ 500 kPa. The Young's modulus of the major components of the SML, smooth muscle cells, is 10–100 kPa. Thus, the EL is supposed to be much stiffer than the SML, and actually, it has been reported that the EL is 2.5 times stiffer than the SML [32]. If the stress-strain relationship is different between the EL and SML, residual stress of the two layers should be different (Fig. 4.16). If the circumferential stresses in the stiff and soft layers are the same in a physiological state, compressive residual stress should appear in the stiff layer and tensile in the soft in an unloaded wall. Such residual stress is not released by the radial cutting. It is well known that the elastic laminae are wavy in an unloaded wall (Fig. 4.17). In contrast, if you look at such a histological section carefully, you will notice that smooth muscle cells remain stretched. The ELs become straight when they are released from the surrounding tissues, indicating their corrugation is buckling caused by the compressive residual stress in the ELs. Stress analyses considering such microscopic residual stress are challenges for the future.

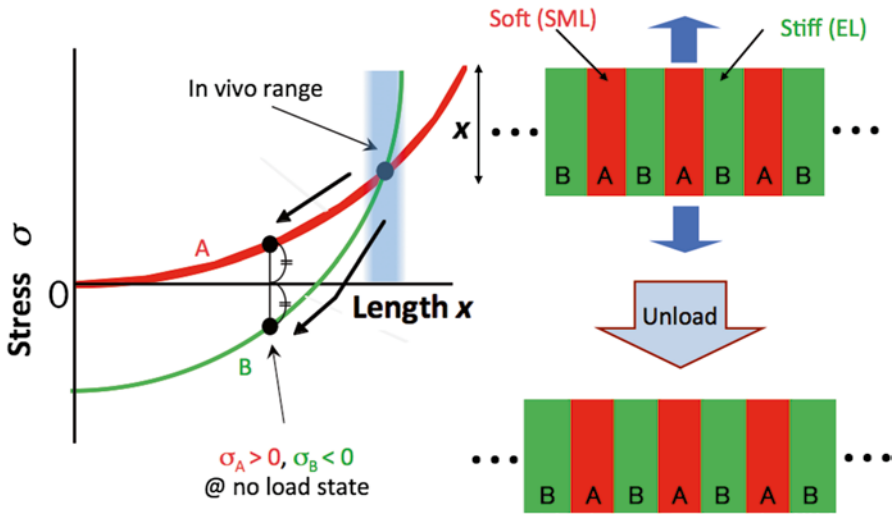
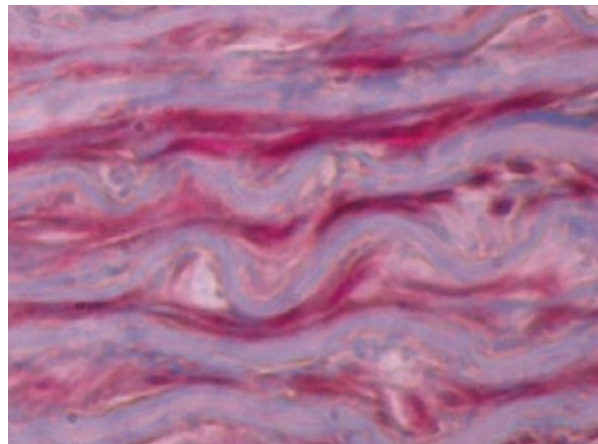


Fig. 4.16 Residual stress caused by mechanical heterogeneity

Fig. 4.17 Corrugated elastic lamina in the unloaded section of porcine thoracic aorta (Reprinted from Ref. [32], with permission from JSME)



4.4 Mechanical Response of Artery Walls

4.4.1 Long-Term Response to Flow Increase

Blood vessel dilates in response to increase in blood flow. This dilation has been reported to be an adaptive response of the blood vessel to maintain fluid shear stress applied to the intraluminal surface at a constant level [33, 34]. Kamiya and Togawa [33] studied the relationship between the blood flow and the radius of the

canine carotid arteries following an operation in which the carotid artery and the jugular vein were connected directly to increase the blood flow in the carotid arteries. Blood flow increased in 3 days after the operation, while the radius of the artery did not change. In contrast, arteries with higher blood flow had larger radius in 6–8 months after the operation. Interestingly, when blood flow in the arteries decreased for some reason, the radius of the artery also decreased. They then studied the relationship between the blood flow and wall shear rate. Wall shear rate was proportional to blood flow in 3 days after the operation because the radius did not change at this time point. In contrast, wall shear rate was maintained at the level before the operation in 6–8 months. This regulation was so powerful that the 3.5 times increase in flow could be compensated. This clearly indicates that the blood vessel wall maintains wall shear rate at a constant level. Wall shear stress is obtained by multiplying wall shear rate with viscosity. Since viscosity of the blood is almost the same among healthy subjects, it can be said that the diameter of blood vessel is regulated to maintain fluid shear stress at a constant level. This response does not occur when endothelial cells are removed from the lumen [35]. Detailed studies revealed that the dilation of the blood vessel in response to flow increase is driven by the endothelial cells. They sense fluid shear stress and secrete various substances causing blood vessel dilation and contraction to maintain the shear stress at a constant level [36].

4.4.2 Long-Term Response to Pressure Increase

Blood vessel wall thickens in response to hypertension. Figure 4.18 shows the relation between histology of blood vessel wall and systolic blood pressure in rats [25] in which Goldblatt hypertension was induced by placing a clip to the renal artery [37]. It is clear that the wall thickness increases markedly in response to blood pressure increase. This wall thickening is believed to be an adaptive response to maintain the circumferential wall stress at a constant level [37–40]. Relationships between the systolic blood pressure and circumferential stress at this pressure are shown in Fig. 4.19 for rats 2, 4, 8, and 16 weeks after the operation. There was no significant correlation between the blood pressure and the circumferential stress even at 2 weeks after the operation. Blood pressure of the rats continues to increase at 2 weeks after the operation and reaches a plateau at ~6 weeks, indicating that the wall thickening occurs very fast in response to blood pressure increase. In contrast, mechanical properties of the artery wall do not change as fast as the circumferential stress does. For example, incremental elastic modulus did not have a significant correlation with blood pressure at 16 weeks after the operation. However, the correlation was significant in 2, 4, and 8 weeks after the operation (Fig. 4.20). These results indicate that not only circumferential stress but also stiffness is restored [40, 41], but restoration of the elastic modulus takes longer time.

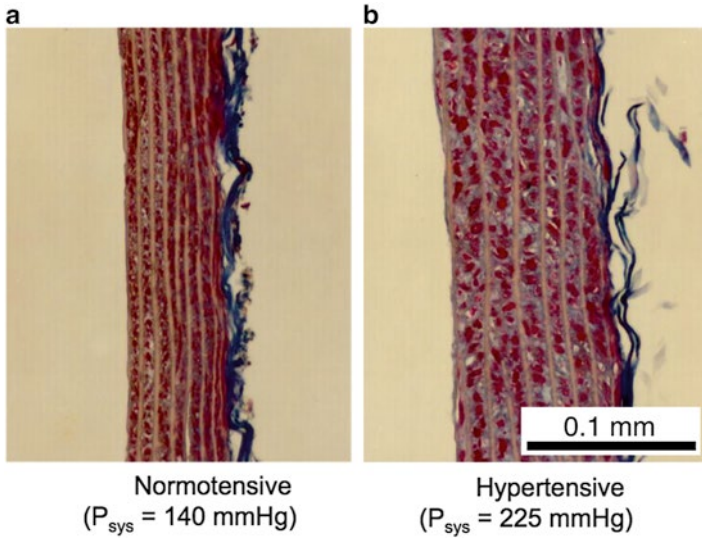


Fig. 4.18 Histological sections of normotensive (a) and hypertensive (b) rat thoracic aorta. Pressure-fixed in each in vivo condition and stained with Azan-Mallory. P_{sys} , systolic blood pressure (Reprinted from Ref. [25], with permission from ASME)

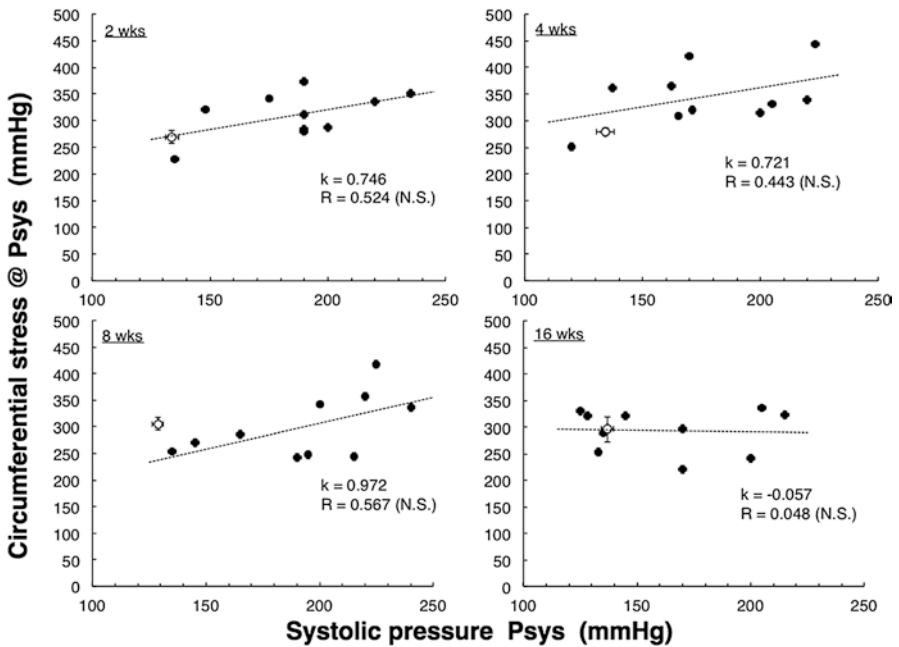


Fig. 4.19 Effect of hypertension on circumferential wall stress of rat thoracic aorta (Reprinted from Ref. [37], with permission from ASME)

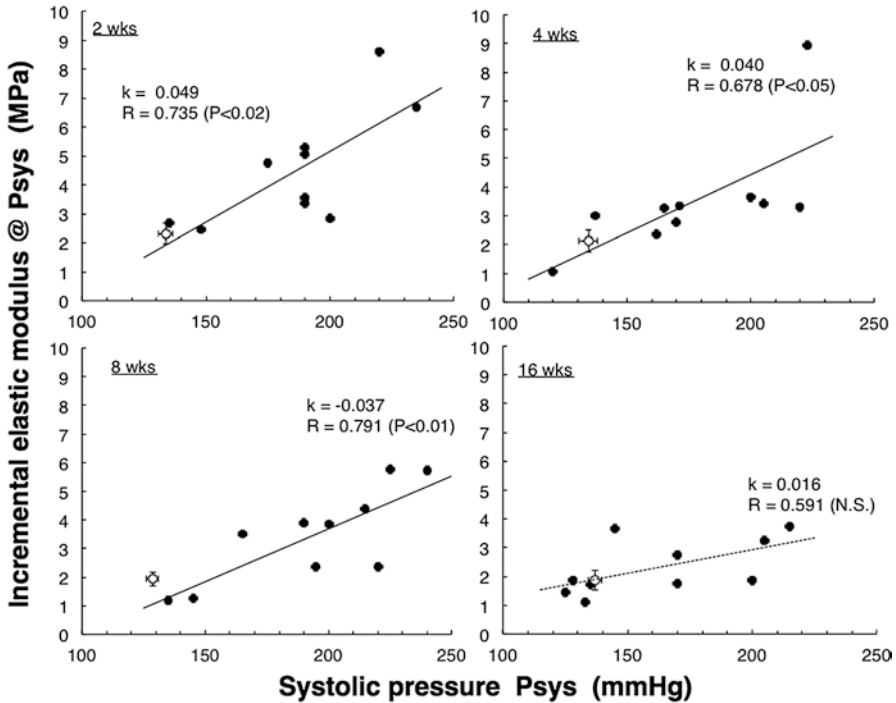


Fig. 4.20 Effect of hypertension on incremental elastic modulus of rat thoracic aorta (Reprinted from Ref. [37], with permission from ASME)

4.4.3 Short-Term Response to Flow Increase

Endothelial cells respond to change in blood flow immediately. For example, they increase the secretion of nitric oxide (NO) within seconds in response to flow increase [42]. NO diffuses into vascular wall and causes smooth muscle relaxation and thus vessel dilation. This dilation may reflect the ability of NO synthesis by the endothelial cells, and has been used to evaluate the endothelial cell function in clinical medicine and is called flow-mediated dilation (FMD) [43]. The brachial artery has been used widely [44, 45] for the FMD measurement. An increase in flow in the brachial artery is achieved by temporal occlusion of the forearm artery by the inflation of a pneumatic cuff placed on the forearm over systolic pressure for 5 min. Upon the release of the cuff, the blood flow in the brachial artery increased sharply, and this results in the increase in the shear stress which activates endothelial nitric oxide synthase to release NO. The NO causes the smooth muscle cells to relax resulting in vasodilatation. FMD is measured as the percentage change in brachial artery diameter from baseline in response to the increased flow. The diameter of the brachial artery is normally measured with an ultrasound probe. Typical example of brachial artery FMD is shown in Fig. 4.21. Dilation of the brachial artery caused by

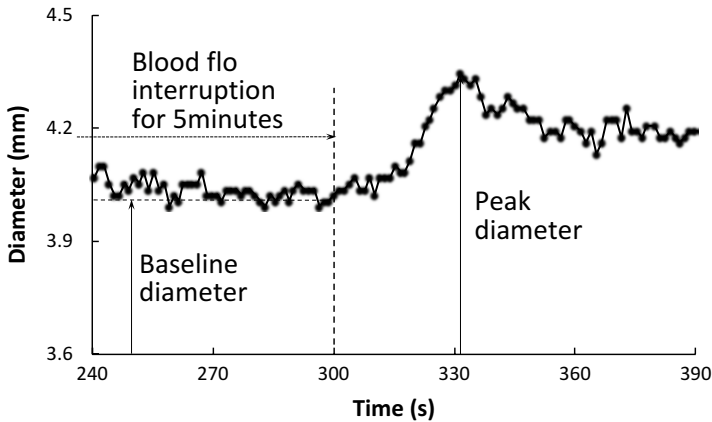


Fig. 4.21 Flow-mediated dilation measured in a human brachial artery

temporal increase in NO is within the range of 5–10 % of the vessel diameter for healthy subjects. FMD test is now one of the most important methods for the diagnosis of endothelial dysfunction and risk of coronary artery disease and other diseases caused by atherosclerosis and is used widely in clinical medicine [46].

4.4.4 Short-Term Response to Pressure Increase

It is well known that the smooth muscle cells show myogenic response, *i.e.*, smooth muscle cells actively contract after they are stretched. This response plays important roles in our body such as autoregulation of blood flow [47]. If the artery wall, especially at the arteriolar level, does not have myogenic response, *i.e.*, the resistance of a vascular bed does not change just like a rigid tube network, blood flow would change in response to change in the arterial pressure (Fig. 4.22a). In reality, blood flow in the vascular bed does not change much in a physiological pressure range (autoregulation, Fig. 4.22b), because slight stretch in the vascular bed due to increase in the arterial pressure causes active contraction of the arteriole and thus reduce the blood flow, and reverse phenomenon occurs when the arterial pressure dropped.

Myogenic response in the vasculature is called the Bayliss effect [48]. Typical example of the Bayliss effect in vascular smooth muscles cells is a response to stretch. When blood pressure is increased in the blood vessels and the blood vessels distend, they react with a constriction. Stretch of the cell membrane opens a stretch-activated ion channel. The cells then become depolarized, and this results in an increase in the intracellular Ca^{2+} ion and triggers muscle contraction. Recently, we have succeeded to observe the Bayliss effect in the brachial artery. We attached an airtight chamber to the upper arm and applied negative pressure in this chamber to

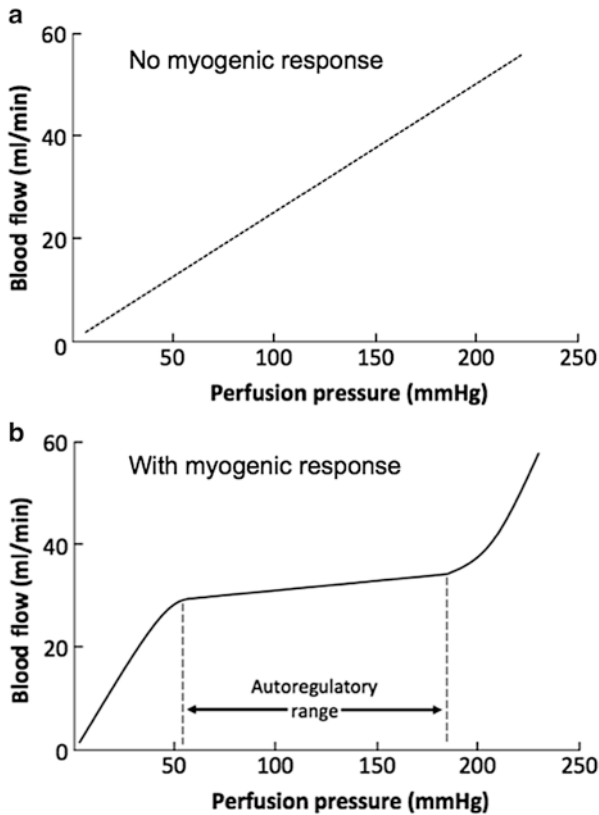


Fig. 4.22 Myogenic response of artery wall

dilate the brachial artery and observed temporal change in the brachial artery diameter with an ultrasound probe. As shown in Fig. 4.23, the artery diameter increased in a stepwise manner upon negative pressure application and then decreased gradually in two minutes. We have named this phenomenon a pressure-mediated contraction (PMC) and are now trying to use PMC as an index of smooth muscle cell function [49, 50].

4.5 Conclusions

Blood vessel is not a simple tube. It is an intelligent pipe which changes dimensions and mechanical properties adaptively in response to changes in blood flow and pressure. It can be said that vascular diseases such as hypertension, atherosclerosis, and aneurysms have a close correlation with the malfunctioning of the mechanical adaptation mechanism. Elucidation of the detailed mechanism of the mechanical

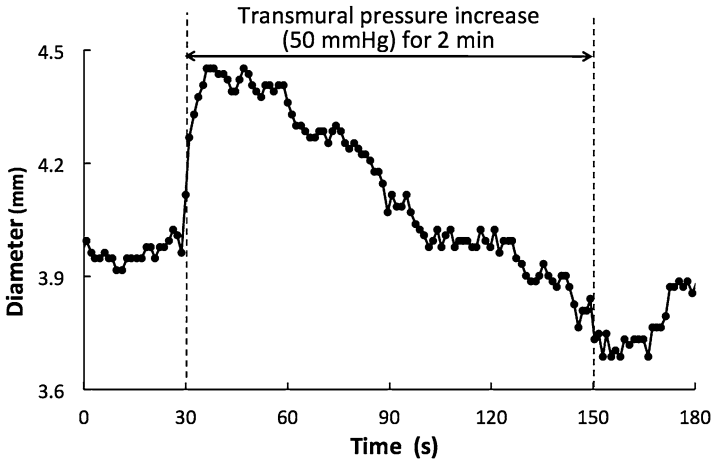


Fig. 4.23 Pressure-mediated contraction measured in a human brachial artery

adaptation of vascular walls may not only help our understanding of pathogenesis of various vascular diseases but also give us various hints in developing new intelligent materials for pipes that can adaptively change the diameter and wall thickness in response to intramural pressure and flow.

Such a mechanical adaptation is driven by the vascular smooth muscle cells in the media. To elucidate the mechanism of the mechanical adaptation, we need to know the mechanical environment of the cells in detail, *i.e.*, at a cellular level and in 3D. As stated in Sect. 4.1, artery wall has a highly complicated structure made of components with various mechanical properties. This indicates that the stress and strain distributions in the blood vessel wall are far from that shown in Figs. 4.11 and 4.15 and highly heterogeneous. Microscopic viewpoint is indispensable in elucidating the mechanism of mechanical adaptation.

Acknowledgements This work was supported in part by the “Knowledge Hub” of AICHI, The Priority Research Project and JSPS KAKENHIs (nos. 22240055 and 24650295 for T.M., 24650256 and 26709002 for S.S., and 24700495 for T.Y.).

References

1. Wolinsky H, Glagov S (1967) A lamellar unit of aortic medial structure and function in mammals. *Circ Res* 20:99–111
2. Urry DW, Okamoto K, Harris RD, Hendrix CF, Long MM (1976) Synthetic, cross-linked polypentapeptide of tropoelastin: an anisotropic, fibrillar elastomer. *Biochemistry* 15:4083–4089
3. Fung YC, Sobin SS (1981) The retained elasticity of elastin under fixation agents. *J Biomech Eng* 103:121–122

4. Matsumoto T, Fukunaga A, Narita K, Nagayama K (2008) Microscopic mechanical analysis of aortic wall: estimation of stress in the intramural elastic laminae and smooth muscle cells in a physiological state. In: Proceedings of the 2008 summer Bioengineering conference (CD-ROM), 192450.pdf
5. Svendsen KH, Thomson G (1984) A new clamping and stretching procedure for determination of collagen fiber stiffness and strength relations upon maturation. *J Biomech* 17:225–229
6. Yamamoto N, Ohno K, Hayashi K, Kuriyama K, Yasuda K, Kaneda K (1993) Effects of stress shielding on the mechanical properties of patellar tendon. *ASME J Biomech Eng* 115:23–28
7. Matsumoto T, Nagayama K (2012) Tensile properties of vascular smooth muscle cells: bridging vascular and cellular biomechanics (review). *J Biomech* 45:745–755
8. Patel DJ, Fry DL (1969) The elastic symmetry of arterial segments in dogs. *Circ Res* 24:1–8
9. Schriebl AJ, Zeindlinger G, Pierce DM, Regitnig P, Holzapfel GA (2012) Determination of the layer-specific distributed collagen fiber orientations in human thoracic and abdominal aortas and common iliac arteries. *J R Soc Interface* 9:1275–1286
10. Roy S, Boss C, Rezakhanlou R, Stergiopoulos N (2010) Experimental characterization of the distribution of collagen fiber recruitment. *J Biomech* 43:84–93
11. Fischer GM, Llauro JG (1966) Collagen and elastin content in canine arteries selected from functionally different vascular beds. *Circ Res* 19:394–399
12. Carew TE, Vaishnav RN, Patel DJ (1968) Compressibility of the arterial wall. *Circ Res* 23:61–68
13. Ohashi T, Sugita S, Matsumoto T, Kumagai K, Akimoto H, Tabayashi K, Sato M (2003) Rupture properties of blood vessel walls measured by pressure-imposed test. *JSME Int J Ser C* 46:1290–1296
14. Sugita S, Matsumoto T, Ohashi T, Kumagai K, Akimoto H, Tabayashi K, Sato M (2012) Evaluation of rupture properties of thoracic aortic aneurysms in a pressure-imposed test for rupture risk estimation. *Cardiovasc Eng Technol* 3:41–51
15. Patel D, Janicki J, Carew T (1969) Static anisotropic elastic properties of the aorta in living dogs. *Circ Res* 25:765–779
16. Biomechanical engineering: a first course. Japan Society of Mechanical Engineers, Maruzen, Tokyo (1997)
17. Bergel DH (1961) The static elastic properties of the arterial wall. *J Physiol* 156:445–457
18. Peterson L, Jensen R, Parnell R (1960) Mechanical properties of arteries in vivo. *Circ Res* 8:622–639
19. Hayashi K, Handa H, Nagasawa S, Okumura A, Moritake K (1980) Stiffness and elastic behavior of human intracranial and extracranial arteries. *J Biomech* 13:175–184
20. Bergel DH (1961) The dynamic elastic properties of the arterial wall. *J Physiol* 156:458–469
21. Cox RH (1979) Contribution of smooth muscle to arterial wall mechanics. *Basic Res Cardiol* 74:1–9
22. Dobrin PB, Rovick AA (1969) Influence of vascular smooth muscle on contractile mechanics and elasticity of arteries. *Am J Physiol* 217:1644–1652
23. Fung YC (1993) Chapter 7: Bioviscoelastic solids, and Chapter 8: Mechanical properties and active remodeling of blood vessels. In: *Biomechanics: mechanical properties of living tissues*, 2nd edn. Springer, New York
24. Humphrey JD (2002) *Cardiovascular solid mechanics: cells, tissues, and organs*. Springer, New York
25. Matsumoto T, Hayashi K (1996) Stress and strain distributions in hypertensive and normotensive rat aorta considering residual strain. *ASME J Biomech Eng* 118:62–73
26. Fung YC, Liu SQ (1989) Change of residual strains in arteries due to hypertrophy caused by aortic constriction. *Circ Res* 65:1340–1349
27. Matsumoto T, Tsuchida M, Sato M (1996) Change in intramural strain distribution in rat aorta due to smooth muscle contraction and relaxation. *Am J Physiol Heart Circ Physiol* 271:H1711–H1716
28. Vaishnav RN, Vossoughi J (1983) Estimation of residual strains in aortic segments. In: Hall CW (ed) *Biomedical engineering II, recent developments*. Pergamon Press, New York

29. Fung YC (1984) Section 2.9: The need for a new hypothesis for residual stress distribution. In: *Biodynamics: circulation*. Springer, New York
30. Takamizawa K, Hayashi K (1987) Strain energy density function and uniform strain hypothesis for arterial mechanics. *J Biomech* 20:7–17
31. Fung YC (1990) Chapter 11: Stress, strain and stability of organs. In: *Biomechanics: motion, flow, stress, and growth*. Springer, New York
32. Matsumoto T, Goto T, Sato M (2004) Microscopic residual stress caused by the mechanical heterogeneity in the lamellar unit of the porcine thoracic aortic wall. *JSME Int J Ser A* 47:341–348
33. Kamiya A, Togawa T (1980) Adaptive regulation of wall shear stress to flow change in the canine carotid artery. *Am J Physiol* 239:H14–H21
34. Masuda H, Zhuang YJ, Singh TM, Kawamura K, Murakami M, Zarins CK, Glagov S (1999) Adaptive remodeling of internal elastic lamina and endothelial lining during flow-induced arterial enlargement. *Arterioscler Thromb Vasc Biol* 19:2298–2307
35. Sugiyama T, Kawamura K, Nanjo H, Sageshima M, Masuda H (1997) Loss of arterial dilation in the reendothelialized area of the flow-loaded rat common carotid artery. *Arterioscler Thromb Vasc Biol* 17:3083–3091
36. Koller A, Sun D, Kaley G (1993) Role of shear stress and endothelial prostaglandins in flow- and viscosity-induced dilation of arterioles in vitro. *Circ Res* 72:1276–1284
37. Matsumoto T, Hayashi K (1994) Mechanical and dimensional adaptation of rat aorta to hypertension. *J Biomech Eng* 116:278–283
38. Wolinsky H (1971) Effects of hypertension and its reversal on the thoracic aorta of male and female rats. *Circ Res* 28:622–637
39. Wolinsky H (1972) Long-term effects of hypertension on the rat aortic wall and their relation to concurrent aging changes. *Circ Res* 30:301–309
40. Vaishnav RN, Vossoughi J, Patel DJ, Cothran LN, Coleman BR, Ison-Franklin EL (1990) Effect of hypertension on elasticity and geometry of aortic tissue from dogs. *ASME J Biomech Eng* 112:70–74
41. Berry C, Greenwald S (1976) Effects of hypertension on the static mechanical properties and chemical composition of the rat aorta. *Cardiovasc Res* 10:437–451
42. Furchgott RF (1983) Role of endothelium in responses of vascular smooth muscle. *Circ Res* 53:557–573
43. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, Deanfield J, Drexler H, Gerhard-Herman M, Herrington D, Vallance P, Vita J, Vogel R (2002) Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. *J Am Coll Cardiol* 39:257–265
44. Anderson EA, Mark AL (1989) Flow-mediated and reflex changes in large peripheral artery tone in humans. *Circulation* 79:93–100
45. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, Lloyd JK, Deanfield JE (1992) Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. *Lancet* 340:1111–1115
46. Cox DA, Vita JA, Treasure CB, Fish RD, Alexander RW, Ganz P, Selwyn AP (1989) Atherosclerosis impairs flow-mediated dilation of coronary arteries in humans. *Circulation* 80:458–465
47. Fung YC (1997) Section 5.13: Local control of blood flow. In: *Biomechanics: circulation*, 2nd edn. Springer, New York
48. Bayliss WM (1902) On the local reactions of the arterial wall to changes of internal pressure. *J Physiol* 28:220–231
49. Matsumoto T, Nagayama K, Takezawa K, Masuda H (2008) US patent application no: 12/071873
50. Yaguchi T, Nagayama K, Tsukahara H, Masuda H, Matsumoto T (2013) Development of a non-invasive multifaceted evaluation system for arterial function under transmural pressure manipulation. International symposium on micro-nanomechanics and human science (MHS2013). doi:[10.1109/MHS.2013.6710460](https://doi.org/10.1109/MHS.2013.6710460)