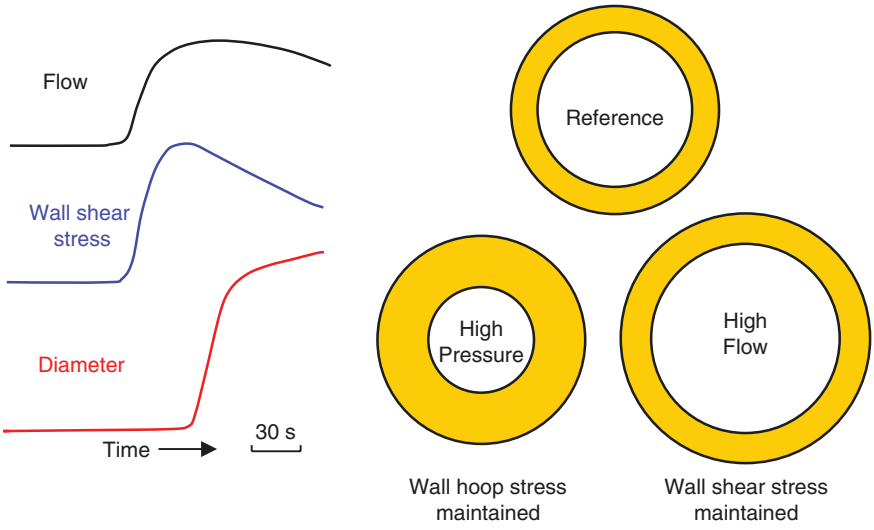
Chapter 29
Mechanotransduction and Vascular Remodeling



Blood vessels respond to pressure and flow, more exactly to hoop stress and wall shear.

Short term. A pressure increase results in a smooth muscle contraction and thus in a diameter decrease, so that hoop stress normalizes (myogenic response, see Chap. 19). A flow increase implies an increase in wall shear stress, which is sensed by the endothelium (glycokalix). The endothelium liberates relaxing factors (e.g., NO) causing dilatation. The increase in diameter reduces the wall shear stress. This is called Flow Mediated Dilation (left panel).

Long term. Sustained high blood pressure implies a high wall hoop stress that leads to wall thickening (hypertrophy), and normalization of hoop stress. Increased flow gives increased wall shear stress and leads to increase in vessel diameter. In general, vascular remodeling leads to a restoration to control levels of hoop stress and wall shear stress (right panel).

N. Westerhof et al., *Snapshots of Hemodynamics*,
https://doi.org/10.1007/978-3-319-91932-4_29

29.1 Description

One of the fundamental characteristics of living tissues is their ability to respond to changes in their mechanical environment.

Although often referred to the macroscopic quantities of pressure and flow, vascular responses are better associated with wall hoop stress and wall shear stress. We recall that wall hoop stress (σ) is related to transmural pressure through the law of Laplace, $\sigma = P/h$ (see Chap. 9), and that wall shear stress (τ) is related to flow, or axial pressure drop, $\Delta P/l$, through the law of Poiseuille, $\tau = 4\eta \cdot Q/\pi r_i^3 = (\Delta P/l)/(r_i/2)$ (Chap. 2).

29.1.1 Short Term Arterial Adaptation

Pressure Effects In the short term, under physiologic conditions, an increase in transmural pressure increases hoop stress, and, via the myogenic response (Chap. 19) of the smooth muscle, vessel diameter decreases and hoop stress is normalized. Thus the increase in vascular tone counterbalances the increased pressure.

Flow Effects Acute changes in blood flow lead to adjustments in vessel caliber, via endothelium-dependent vasodilation or vasoconstriction. A flow increase, leads to an increase in wall shear stress, which is sensed by the endothelium, and followed by vasodilation. Vasodilators, e.g., NO, are released and the smooth muscle relaxes. Muscle relaxation results in vasodilation and increase in vessel diameter, thereby normalizing the shear stress. In Chap. 2 we mentioned that wall shear stress is neither the same in similar vessels in different mammals, nor the same in different vessels in a single animal. Yet it appears that local endothelial cells have a desired set-point of shear stress.

Axial Effects The mechanical behavior of the arterial wall is dominated by three stresses: flow induced wall shear stress and the circumferential and axial components of the pressure-induced intramural stress. These stresses regulate the three most important geometric properties of an artery: its luminal radius, its wall thickness, and its axial length. But while radius and wall thickness are relatively easy to measure *in vivo*, axial length is more difficult to pin down. Nevertheless, an increasing amount of evidence seems to indicate that the arterial wall compensates an increase in intramural pressure not only via circumferential remodeling but also via a reduction in axial stretch, thus increasing its unloaded length [1].

29.1.2 Mechanotransduction

Mechanotransduction refers to the many mechanisms by which cells convert mechanical stimuli into chemical activity. One such mechanism is flow-induced vasorelaxation, whereby increased wall shear stress causes smooth muscle relaxation, (Figure in the Box, at left).

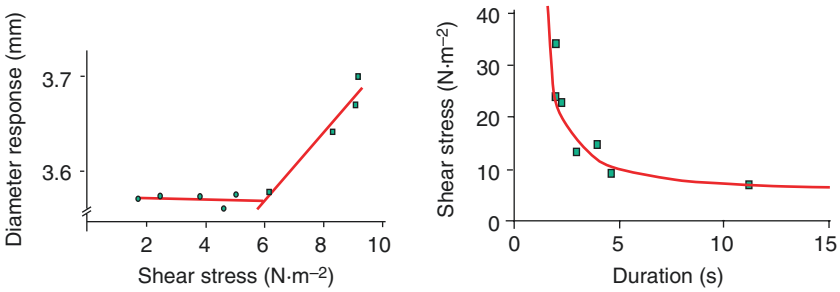


Fig. 29.1 The diameter response relates linearly with shear stress, above a threshold value (left panel). Strength (stress magnitude) and duration of the stress determine the response to shear stress. They relate inversely, like a strength-duration curve (right panel). (Adapted from [4], by permission)

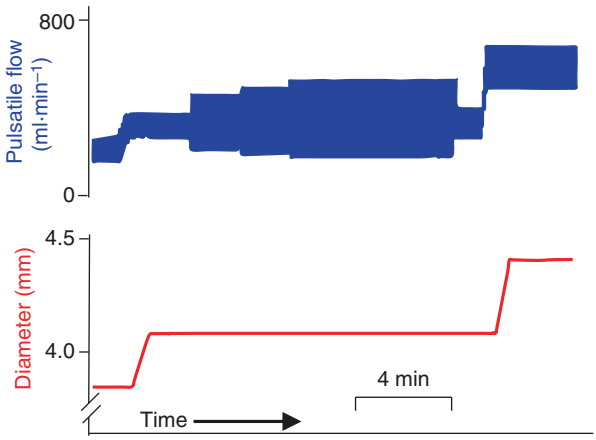


Fig. 29.2 An increase mean flow (top trace) induces an increase in diameter (bottom trace), as shown in the early part of the tracings. The subsequent increase in the pulsatility of flow, at the same mean flow, has no detectable effect on diameter. A further increase in mean flow induces the final increase in the diameter (last part of the tracings). (Adapted from Ref. [4], by permission)

This aspect of mechanotransduction only takes place when the endothelium is intact. The search for the mechanism was based on the finding by Furchgott that Acetylcholine, ACh, only relaxes the smooth muscle if the vascular endothelium is intact [2]. The factor liberated by the endothelium was named Endothelium Derived Relaxing Factor, EDRF [2]. Palmer et al. showed that EDRF is Nitric Oxide NO, a small molecule that also plays a role in synaptic transmission [3]. Thus in shear rate dependent dilation NO plays a major role as a dilating factor. The shear stress needs to be higher than a certain threshold value before diameter changes occur (Fig. 29.1, left). The level of the stress, and its duration, need to be of sufficient magnitude to elicit a response (Fig. 29.1, right). This is a relation akin to the strength-duration curve defining the response of nerve tissue. Also it has been shown that it is mainly the mean shear stress that causes vasodilation and not the magnitude of oscillations about the mean stress (Fig. 29.2). Shear stress dependent arterial dilatation is abolished by the NO synthesis inhibitor L-NAME, by hyaluronidase, and by intraluminal hyperglycemia.

At present, it is accepted knowledge that the glycocalyx (a gel layer 0.5 μm thick between the endothelium and the blood in the lumen) is the main sensor of changes

in shear stress. However, many different transmembrane and intracellular mechanosensors have been reported, including G protein–coupled receptors, ion channels, plasma membrane phospholipids, receptor tyrosine kinases, caveolae, integrins and their basal adhesion complex or platelet endothelial cell adhesion molecule-1 (PECAM-1) and its associated intercellular junction complex [5, 6]. Mechanotransduction of shear force is not restricted to the luminal membrane but has also been observed at remote sites via propagation of forces through the cytoskeleton [7].

29.1.3 Long Term Vascular Adaptation

Growth and remodeling are processes that allow the living tissue to maintain an optimal environment under physiological development (Chap. 2) as well as under various pathologic conditions. The arterial wall responds to prolonged changes in transmural pressure or flow by means of geometrical adaptation (e.g., hypertrophy), structural adaptation (e.g., change in scleroprotein content, stiffening) and functional adaptation (e.g., changes in endothelial function or vascular smooth muscle tone).

Pressure Effects In the long term an increase in pressure leads to a thickening of the arterial wall (hypertrophy). Wall thickening lowers wall hoop stress down to control (normotensive) levels, thus counterbalancing the increase in pressure. An example of such adaptation is shown in Fig. 29.3.

Flow Effects Chronic changes in flow lead to remodeling. Long-term, flow-induced remodeling implies reorganization of cellular and extracellular wall components. The adaptive response to changes in blood flow has been studied in various animals and it was found that the vessel inner diameter adapts to preserve the level of wall shear at the intimal surface. Kamiya and Togawa [9] first demonstrated that the adaptive response to an increase in flow leads to normalization in wall shear stress. They constructed an arterio-venous shunt between the carotid artery and jugular

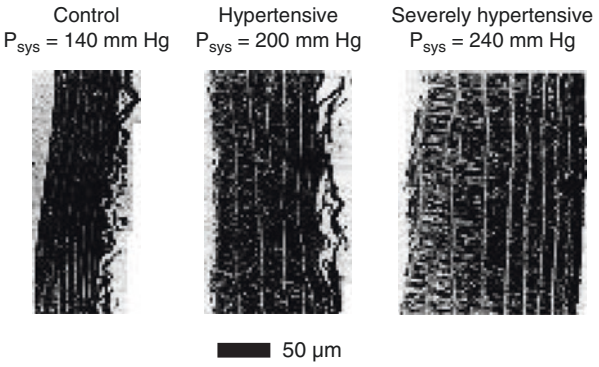


Fig. 29.3 Thoracic aortas of rats fixed under their in vivo pressure and stained with Azan. Sections are parallel to the longitudinal axis of the vessel with the intimal surface facing leftward. (Adapted from Ref. [8], by permission)

vein of a dog, which led to a significant increase in blood flow in the ipsilateral carotid and a decrease in blood flow in the contralateral one. Six to eight months after the operation, carotid diameter was increased in the segment with high flow and decreased in the segment with low flow. The diameter change preserved wall shear stress within 15% of the pre-operation levels, despite the severe increase or decrease in flow. Similar findings were reported by Langille [10] on the rabbit carotid artery, where a reduction in flow led to a reduction in internal diameter and restoration of wall shear stress (see Fig. 29.4). Remodeling in response to increased flow appears to be associated with cell hyperplasia, structural changes in internal elastic lamina and adventitia as well as with the contractile properties of the artery. The endothelium and nitric oxide synthesis are the main mediators in the vessel adaptation to flow. For example, inhibition of nitric oxide synthesis totally abolishes the capacity of the pig carotid artery to remodel and maintain control levels of wall shear in the presence of an arterio-venous shunt [11].

Axial Effects Van Loon et al. [12] showed that during *ex vivo* experiments the axial force increases with pressure if the artery is held at an axial stretch above its *in vivo* value and decreases with pressure if the artery is stretched less than it was *in vivo*. However, when the artery is stretched exactly as it was *in vivo*, the axial force needed to keep it in place does not depend on pressure. This discovery demonstrated for the first time that axial stress is inherent to the microstructure of the artery and is not governed by peripheral tethering [1, 12]. The adaptive axial response to changes in blood flow or pressure has been investigated in several animal studies. When rabbit cerebral arteries [13] or carotid arteries [14] are exposed to a sustained increase in blood flow they respond with a significant lengthening that can result in gross tortuosity. Jackson et al. showed that an artificially imposed extension of the

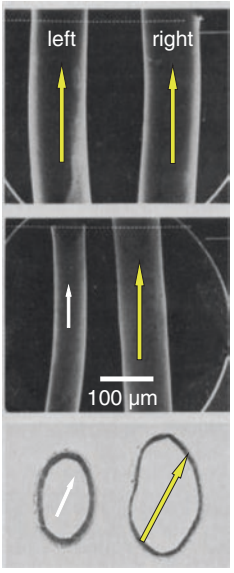


Fig. 29.4 Scanning Electron micrographs of methacrylate casts of left and right common carotid arteries of a normal rabbit (top) and after 2 weeks after left carotid flow was reduced (middle), as indicated by white arrow. Cross-sections after 2 weeks of left common carotid flow reduction are given in the bottom panel. (Adapted from Ref. [10], by permission)

carotid artery in rabbits results in adaptive *in vivo* remodeling, with synthesis of additional extracellular matrix until the original *in vivo* stretch has been restored [15]. Eberth et al. used a model in which the aortic arch was transversally banded in order to induce a local increase in pulse pressure in the right but not the left common carotid artery. Biaxial force-length tests showed that the *in vivo* axial stretch was significantly lower in the right carotid artery than in the left while circumferential stress-stretch behavior was similar in both carotids, thus providing indirect evidence for an effective axial compensation mechanism [16].

29.1.4 Residual Stress in Relation to Growth and Remodeling

In Chap. 10 it was mentioned that both cardiac tissue and vascular tissue are not at a zero stress state when all loads are removed [17]. It was also postulated that residual stresses help maintain a uniform stress distribution across the wall (Chap. 10). When, for different physiological or pathological reasons, the biomechanical environment to which the wall is subjected is changed, mechanical stresses within the arterial wall will also be altered and their distribution will not be uniform. A remodeling process will likely take place in order to restore stresses and strain to control levels.

Remodeling leads to changes in geometry and structure, with addition or resorption of mass. Consequently, the zero stress state will change. Changes in the zero stress state, or changes in the opening angle allow for the monitoring of arterial wall remodeling. Figure 29.5 shows changes in wall thickness and opening angle in various positions along the aorta of rats, which received a very tight banding of the thoracic aorta just below the diaphragm. For the aorta above the banding site, which was exposed to higher pressure, we observe a progressive thickening of the aortic wall during the entire post-surgery period (normalization of hoop stress). The opening angle, however, shows a non-monotonic evolution. Initially, the opening angle increases, indicative of higher growth in the internal wall layers. Later, as the wall thickens and stress levels are restored, the opening angle returns to control levels as

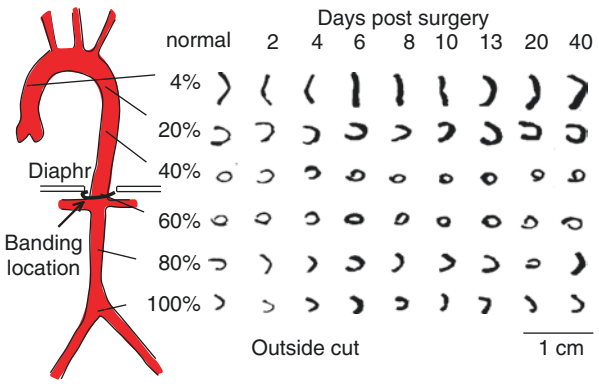


Fig. 29.5 Photographs of aortic rings cut open radially to reveal their zero stress state (ZSS). The first column shows the ZSS in normal rats. The other columns show the change in ZSS after hypertension was induced by banding of the aorta above the coeliac trunc. (Adapted from Ref. [17], by permission)

well. The initial higher growth in the internal wall layers is reflected by the increase in opening angle. This demonstrates that remodeling is dependent on the local stress distribution and also that wall remodeling affects the residual stress distribution within the arterial wall.

29.2 Physiological and Clinical Relevance

29.2.1 Arterial Remodeling in Hypertension

In presence of essential hypertension, vascular resistance increases due to alterations in resistance vessel architecture, decrease in lumen diameter and increase in media thickness/lumen diameter ratio. This corresponds to an inward eutrophic remodeling, as schematically shown in Fig. 29.6. The type of remodeling in resistance vessels depends on the type of hypertension and treatment. Human renal hypertension leads to inward hypertrophic remodeling. During anti-hypertensive treatment the situation is often reversed and outward eutrophic remodeling and hypertrophic remodeling is observed. Figure 29.6 shows the different types of remodeling that can be distinguished, as suggested by Mulvany [18].

29.2.2 Arterial Remodeling in Hypertension: Large Arteries

Remodeling due to hypertension is known to increase wall thickness and restore wall hoop stress. In terms of compliance and elastic properties, arterial remodeling tends to be vessel specific. Aortic and carotid artery compliances are reduced in

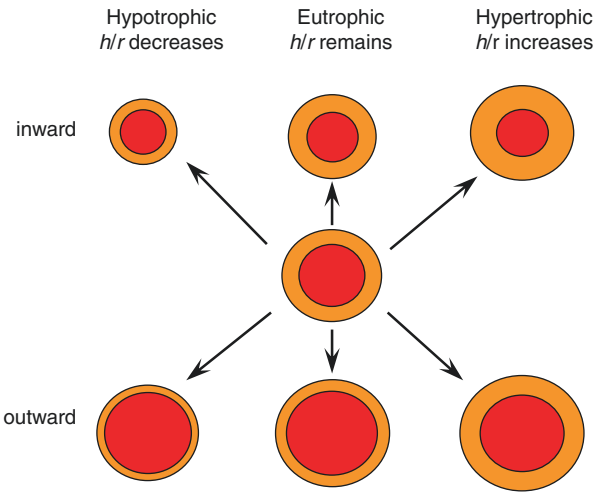


Fig. 29.6 Classification of different types of arterial remodeling, i.e. a structurally determined change. (Adapted from Ref. [18], by permission)

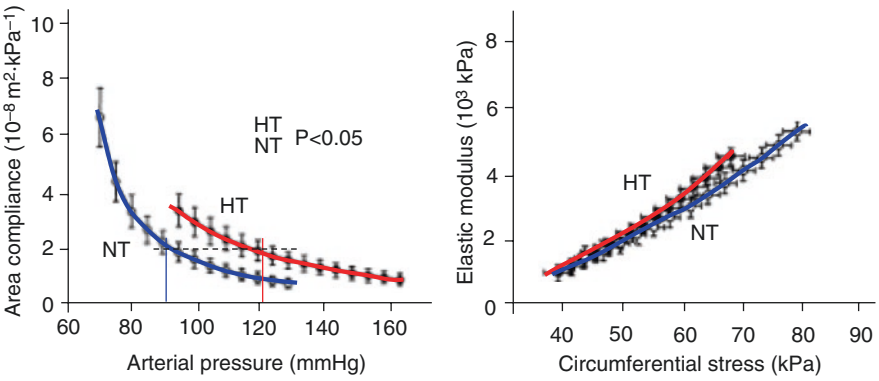


Fig. 29.7 Radial artery area compliance (left) and elastic modulus (right) measured in vivo in a group of normotensive (NT, n = 22) and hypertensive subjects (HT, n = 25). When compared at their corresponding mean operating pressures (NT: 90 mmHg; HT: 121 mmHg) area compliance was similar despite significant concentric hypertrophy (left panel). In normotensive subjects wall thickness is 0.28 mm compared to 0.40 mm in hypertensive patients. Internal diameter is the same and equal to 2.50 mm in both groups. The incremental elastic modulus-stress curve (right panel) was essentially the same in normotensives and hypertensives, suggesting similar tissue material properties in the two groups. (Adapted from Ref. [19], by permission)

hypertension. Radial artery compliance and incremental elastic modulus (Fig. 29.7), however, seem to be preserved in hypertensive patients [19]. It is important here to acknowledge the nonlinear nature of the compliance and elastic modulus curves. Compliance is expressed as a function of pressure (structural property) and elastic modulus as a function of stress or strain (material property). We observe that at their corresponding operating pressure, normotensive and hypertensive radial arteries exhibit the same compliance, which is indicative of some kind of structural remodeling aiming to maintain normotensive compliance levels. Further, the incremental modulus-stress curve is identical in normotensive and hypertensive patients, which means that the intrinsic elastic properties of the wall material remained the same. This example demonstrates nicely the capacity of the radial artery to remodel in hypertension in a manner that normalizes wall stress by thickening, maintains control compliance levels despite exposure to higher pressure and preserves the intrinsic elastic properties of the arterial tissue.

29.2.3 Flow Mediated Dilatation, FMD, as a Means to Evaluate Endothelial Function

Metabolic vasodilatation within an organ supplied causes a fall in peripheral resistance so that blood flow in the artery supplying the organ increases (Figure in the Box, top trace). The increased flow causes an increase in wall shear stress (middle trace). The mechano-sensor within the arterial wall, the endothelium, detects the

wall shear and produces arterial dilatation, so that the increased flow required downstream is accommodated and wall shear stress normalized. The vasodilation is mediated by the endothelium-dependent relaxing factor nitric oxide (NO). The response is abolished if the animal is pretreated with a NO synthase inhibitor or when the endothelium is removed or made nonfunctional. The increase in diameter in the supply artery is called Flow Mediated Dilatation (FMD).

Flow Mediated Dilatation can be studied noninvasively in arteries. For instance, brachial artery diameter can be measured during control and during post-occlusion reactive hyperemia where flow is increased. The increased wall shear stress causes endothelium dependent dilation which can be measured noninvasively (Ultrasound, Wall tracking). An endothelium independent vasodilator, (e.g., sublingual glyceryl trinitrate, GTN), is used to test muscle relaxation of the artery without involvement of the endothelium [20, 21].

29.2.4 Low Shear and Atheroma

According to Caro [22], and substantial subsequent literature, atheromatous plaques develop preferentially at sites with low shear. Different hypotheses as to why this is the case have been debated, but it is generally accepted that shear responsive genes are upregulated at low shear regions, thus making these regions more welcoming for inflammatory cells through an increased expression of adhesion factors [23]. A more detailed analysis of the role of shear stress in atherosclerosis is discussed in Chap. 30.

It can also be appreciated why diabetic patients and people with glucose intolerance have accelerated athero-thrombotic disease, as the hyperglycemia inhibits the production of NO in response to shear stress [24]. Hyperinsulinaemia occurs in patients pre-disposed to type-2 diabetes (metabolic syndrome or insulin resistance) and may occur with excess insulin administration in type 1 diabetes. The hyperinsulinaemia results in more dilated arteries than normal, and therefore shear stress is lower than normal (shear stress is inversely related to the radius to the third power, see Chap. 2). Thus diabetic hyperinsulinaemia creates an arterial tree with overall low shear stresses, predisposing to atheroma, and the accompanying diabetic hyperglycemia also inhibits the response to increased shear as generated by exercise, further predisposing the patient to arterial lesions.

Axial stress and bypass grafts The fact that it is near impossible to estimate axial quantities from *in vivo* makes it difficult to illustrate the effect of axial stress on arterial remodeling with clinically relevant examples. One potentially important application is the fact that an artery that has been bypassed by a graft, e.g. after surgical intervention due to aortic aneurysm or coronary artery disease, will usually experience an altered axial stretch. A computational model of a bypassed graft has demonstrated that abnormal circumferential and axial stresses in the vicinity of the stent-graft anastomosis cause wall thickening that tends to restore the stress state such that it approaches the stress state existing further from the clamped area [25].

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