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Elements of Vascular Mechanics

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1. Introduction

Between half and two thirds of human mortality in developed countries can be attributed to vascular diseases. Financial losses, human sufferings are increasing with aging of the population. Vascular diseases develop when some or many vessels in the body are unable to fulfill their functions. The main function of blood vessels is essentially a mechanical one: to conduct blood. Vessels are functioning in a unique in the body mechanical environment: they are continuously subjected to hemodynamic forces: to shear stress of flowing blood and to distending forces of pressure of the blood in the lumen. Vessels are so much adapted to these hemodynamic forces that it is impossible to understand their physiology, pharmacology and pathology without taking into consideration the unavoidable biomechanical steps in the complicated pathways of cellular and systemic physiological vascular feed-back control loops, to understand vascular drug action and pathomechanism of vascular disease (Lee 2000).

Biomechanics is thus at the very core of all vascular sciences. That is reflected in the high number of papers published in the area. 35 000 papers listed in the Ovid Medline between 1948 and 2010 included knowledge on vascular mechanics in its narrower sense (excluding papers dealing only with physiological and pharmacological means of vascular smooth muscle control). Deteriorating Windkessel function of the aged, of the chronic hypertensive, even after effective treatment of mean arterial pressure, geometric, biomechanical consequences of atherosclerotic focal remodeling of large arteries, contractile and elastic remodeling of resistance *arteries* with aging, with hypertension and with diabetes, remodeling of venous networks and the venous wall in chronic venous disease, inevitably draws the attention of clinicians and of pathologists to biomechanical questions. Recent developments in vascular mechanics, backed with many methodical improvements in the field (Berczi 2005, Cox 1974, Duling 1981, Huotari 2010, Mersich 2005, Nadasy 2001, Shimazu 1986, See Fig. 1.), integration of these results into the context of reliable older knowledge makes now a systemic overview of the most important aspects of vascular mechanics possible. We will see that an almost axiomatic approach to a phenomenological description of vascular biomechanics is now in sight. Methodical advancement in the field of cellular physiology, histochemistry and biochemistry (Discher 2009) identified many if *not all extra- and intracellular fiber types and molecules* contributing to the biomechanics of the vascular wall. Mechanical factors in intra- and extracellular fiber protein expression control are just being identified. The emerging debate whether mechanics or biochemistry controls vascular

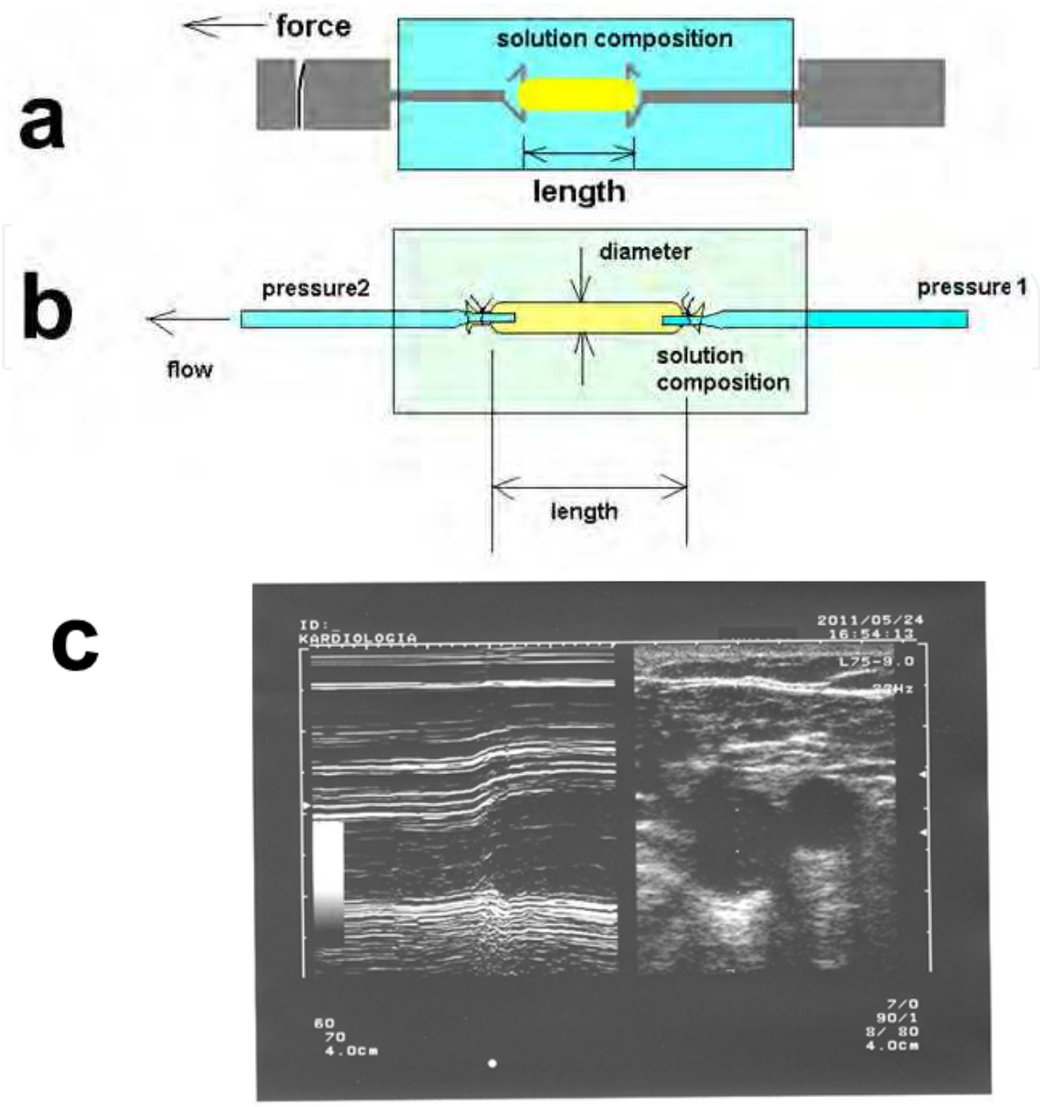

Fig. 1. Some methodics of vascular mechanics. a. In vitro wire myography. Circumferential vascular rings and strips are mostly studied. Frequently applied for isometric measurements of active forces in response to different vasoactive substances. Elasticity and tensile strength can also be studied. Geometric measurements (strip width and thickness) are needed to compute stress and to compare the situation with in vivo pressure loads. b. In vitro pressure arteriography. Cylindrical segments are mounted on cannulas in a glass-bottomed tissue bath. Devices have been developed both for macroscopic and microscopic vessels. Intraluminal pressure and flow can be altered to mimic in vivo situation, outer and inner diameters are measured optically. Mostly pressure-diameter plots are taken at different levels of smooth muscle tone, or diameter alterations are recorded at continuous pressures in response to vasoactive substances. c. In vivo ultrasonographic measurement of vascular lumen changes for biomechanical computations. Right, B-mode record of common femoral artery and vein. Left, elastic dilation of common femoral vein diameter in response to a controlled Valsalva attempt. M-mode record (as a function of time, courtesy of dr AÁ Molnar and of prof V Bérczi).

protein expression, we believe, is meaningless if the question is approached from the point of view of system physiology. Mechanical forces from hemodynamics can induce transmitter release, which, in turn might close the physiological control loop by acting back on hemodynamics. Or, biologically active substances inducing alterations in local tissue function, might, at the same time induce vascular changes supporting or just speeding up other existing vascular control loops adapting tissue circulation to altered tissue function. Such "feed-forward" loops are very common in physiology. We believe, that in many cases derailment of such optimized control processes in a situation that could not be phylogenetically expected, will be the reason for the observed "pathological effect" visibly acting against biomechanical control (Safar 2005). What is still missing now, is the mechanics at the molecular level. *The low-energy level steric deformations of force-bearing molecules*, determining the phenomenologically descriptionable mechanical behavior are not known, maybe, with the single exception of actomyosin crossbridges of vascular smooth muscle cells.

2. Biological background of vascular mechanics

2.1 Separation of the vascular space

The *closed vascular system of vertebrates* ensures fast nourishment of large neural and muscle masses, and fast exchange of materials in gills, lungs, kidneys, liver and intestines (Schmidt-Nielsen 1979). The term "closed" means, that blood vessels are lined internally with a fairly continuous endothelium (some exceptions do exist). Blood cells in vertebrate tissues are not forced to uncertain, zigzagging routes in extracellular space among neighboring cells (as e.g. in many worms), they will move through tissues not leaving the lumen of preformed vascular tubes (again, situations with exceptions do exist). Lesser friction makes faster blood flows possible with the same energy expense.

2.2 Distribution of blood flow in space: the network geometry

While diffusion routes of substances from blood to cells are by confinement of blood into vessels somewhat increased, owing to the rich network of minute capillary vessels few cells in the body will be farther than about a hundred micrometers from a neighboring small vessel. Such small exchange vessels, the capillaries should be very narrow and large in number to ensure optimal diffusion, and this increases friction of blood in them. This is minimized by the very specific molecular structure of both the luminal surface of the endothelial cell lining and of blood cells, ensuring easy sliding along each other. Friction is also limited by the fact that larger distances are traveled by the blood in larger vessels. Getting closer to their target tissues such larger vessels (arteries) will divide into smaller and smaller branches, finally forming the capillaries. Capillaries will be collected again by repeated confluences into larger vessels, the veins. That is the basic principle how *vascular networks* are built. We can also easily recognize that such a geometry ensures that blood flow to each piece of the body can be separately controlled by adjusting the diameter of the minute vascular tubes leading to it (Abramson 1962, Cliff 1976, Schwartz 1980).

2.3 Distribution of blood flow in time: periodic pump and elastic pressure reservoir

Convection of blood in tubes with real friction can be maintained by continuous investment of mechanical energy. In many lower animals, a peristalsis-like movement of the blood

vessel wall propagates blood in the vascular system, but in all vertebrates, motoric force is centralized at a discrete site of the circulation, the heart. Vessels leading away from the heart toward the tissues will be the *arteries*, and vessels leading and emptying the blood back into the heart will be the *veins*. Motoric force of the heart is produced by the heart muscles. Rotational pumps might be the solution for modern left ventricular assist devices, heart chambers with muscular walls could produce pumping force only in two phases, filling and ejection, which means that pressures and flows produced are inherently periodic. Periodic flow in tubes is highly uneconomic. This problem is circumvented by the *elasticity* of the vessels, especially of those close to the heart. These are filled with blood during the ejection period of the heart, and they press the blood forward by their elastic contraction while the pump is idle during its filling phase (see *Windkessel* function). Higher blood flow means the possibility of a higher tissue metabolism, higher speeds of muscle contraction, higher rates of neural, renal, splanchnic and skin functions, all advantageous for the individual. To press viscous blood through a system of microvessels needs a pressure difference. The less is the tissue's hydrodynamic resistance and the higher is the difference between inlet and outlet pressures, the higher the tissue flow will be. Diffusion will be optimal from a set of very narrow vessels. That determines a certain resistance for the capillary segment of the circulation. Such adaptation took place in the pulmonary circulation of mammals where vascular resistance outside the pulmonary capillaries is negligible. An other possibility to elevate tissue blood flow is to elevate the pressure head. In the systemic circulation of vertebrates outlet pressure, that is venous pressure, cannot be further decreased, as blood returning to the heart has close to atmospheric pressure. Arterial pressure, however, seems to be increasing in more developed forms of vertebrates, mammals having higher arterial pressures than reptilians, amphibians and fishes (Altman 1974, Schmidt-Nielsen 1979, Schwartz 1980).

2.4 Economic and independent control of blood flow in space and in time: resistance arteries and further elevation in blood pressure

But surprisingly, not all the energy provided by high arterial pressures will be used up to keep tissue flows at high levels. Substantial part of this energy will be lost, seemingly useless, in a short segment of the arterial circulation, in the *resistance arteries*. In healthy humans the mean arterial pressure of approximately 95 mmHg of larger arteries (inner diameters over 1 mm) will be halved in the small arteries and arterioles (inner diameters from 600 μm down to about 20 μm), pressures in the arterial side of the capillaries being around 40 mmHg. What might be the advantages of such a situation? For economic reasons, tissue blood flow should be adjusted to metabolic or other physiological needs. E.g. working muscle requires 30-50 times larger flow per unit mass than in the resting state. Large difference between maximum and minimum blood flows will be characteristic also for the splanchnic, renal and skin circulations. The solution is that in resting tissue small arteries will have smaller lumina due to continuous *smooth muscle contraction*, which can be dilated quickly as tissue needs increase, increasing local flow. Dilatation of a larger population of such resistance arteries should induce the collapse of pressure in the arteries, with collapse of blood flow to many parallelly connected tissues and organs. To ensure their blood flow they should also dilate to a certain level, further decreasing arterial pressure, again, with further needs for adjustments in all vessels of the body. A relative high, controlled *mean arterial pressure*, however, provides a pressure reservoir, from which all capillaries are

supplied through a control segment of the resistance arteries (Abramson 1962, Cliff 1976, Milnor 1982, Nadasy 2007a). The mean arterial pressure in the reservoir is then controlled by feed-back mechanisms, adjusting heart pumping function and actual levels of overall peripheral hemodynamic resistance. And now we can reach the conclusion that by this mechanism, very high blood flows can be provided for functioning tissues, with a certain independence from affecting the circulation of other organs and tissues.

2.5 The price: unceasing pulsatile stress on the arterial wall

We needed that flow of reasoning to touch on a central problem of mammalian biology, which is a biomechanical one: *The wall of the arteries will be subjected to continuous and periodically changing forces arising from the pulsatile arterial pressure throughout the life* of the individual. This is a very specific problem in animal biology (Toth 1998, Nadasy 2007a, 2007b). Hearts should beat continuously, but the periods between two contractions (diastole) guarantee some time for biochemical, metabolic and circulatory recovery. The same can be told for periodic contractions of skeletal muscle and subsequent tendon loads and for the compression forces in bone and cartilage. But the artery wall can never get rid of the effect of the hard distending pressure and its periodic systolic elevations. All components of the wall had to accommodate to the omnipresence of distending forces. One possibility to reduce force per square millimeter section of the wall, on individual vascular constituents is to increase the thickness of the wall. The aortic wall, with about six times higher pressures is much thicker than that of the pulmonary trunk. Thicker wall means larger diffusion distances to nourish the artery wall itself. Diffusion in case of large arteries will not be sufficient, the supplying vessels (vasa vasorum) should enter the wall. Still the innermost layers of the large arteries will be avascular, as the pressures in the wall would compress any vasa vasorum in it. Avascular tissues are but a few in the mammalian body, comprising geriatrically hectic areas (tooth enamel, eye cornea, lens, article hyaline cartilage).

2.6 Force-bearing histological elements of the wall

A substantial part of the periodic stress due to the pulsatile component of the blood pressure will be met by the *elastic membranes* (Apter 1966). Their amount is high in arteries close to the heart, decreasing toward the periphery and diminishing in the smallest arteries with inner diameters below about 120 μm (true arterioles). The other connective tissue component, *collagen* lends rigidity and high tensile strength to the wall. Still there is some mystery about the omnipresence of *smooth muscle* in the aorta and in the large arteries. Contraction (reduced circumference) in these vessels is not extensive, and if any, it will hardly affect blood flows in such large vessels. It is widely accepted, that their tone sets optimal *elasticity* of the artery wall. Contracting, they strengthen the cytoskeletal elements (*intermediate, actin and myosin filaments*) in the wall. These cells thus are among the parallelly and serially connected force-bearing elements of the vascular wall. The *dense bodies* are forming a lattice network with *intermediate filaments connecting* them. Parallel bunches of thin (actin) filments attach also to the dense bodies and to the *hemidesmosomes* of the smooth muscle membrane. *Thick (myosin) filaments*, interconnect opposing actin filament bunches, and with the ATP-fueled *actomyosin crossbridges* can pull them closer to each other. Active slide of actin and myosin filaments upon each other ensures thus smooth muscle contraction. Vascular smooth muscle, can characteristically form very slow cycling of cross-bridges even at

actively shortened length, yielding the typical *latch contraction* (Rhee 2003, Somlyo 1968). And it can be proven that at least part of vessel wall *viscosity* has to be attributed to passive slide in their contractile apparatus. All smooth muscle cell is surrounded by a basement membrane. In addition, several proteins of the mechanical transmission between intra- and extracellular fibers and filaments forming the *mechanical anchoring structures* have been identified (Clyman 1990, Gabella 1984).

In resistance arteries, however, contraction of smooth muscle will massively affect blood flow to the affected territory. The relative thick wall of these vessels will result that a relative slight contraction of a circumferentially positioned smooth muscle cell at the outer surface will induce a much more effective reduction in the inner radius.

3. Mechanics of solid materials and fluids – their applicability for vascular mechanics

Blood vessels are subjected to general laws of physics and mechanics, several of the parameters applied to study non-living material and several of the general mechanical laws find a broad application in the field of vascular mechanics (Bergel 1961, 1964, Fung YC 1984, Gow 1972, Monos 1986). We must not forget, however, that *vascular (living) tissue is one of the most complicated semi-solid materials ever studied by specialists*. There are some specific characteristics rarely found in non-living material. Such is the build-up of the whole structure under conditions of periodic and continuous distending and shear forces. The geometry of the specimens, the amount, quality and direction of force-bearing fibers, their mechanical interconnections with each other specially adapt to the in vivo occurring mechanical forces. The *force bearing elements in the vascular wall are mostly fibers, arranged in direction of the forces, able to bear pulling forces only*. Pushing forces are rare in the wall, maybe they can be produced from compression of closed, deformable fluid compartments and after pathologic calcification of the tissue. That complicates the understanding of cyclic viscoelastic events. How then, elongation of viscous units can be restored? The ability, never seen in non-living material, to *produce active stress at the expense of chemical energy is the solution*. And in all mechanical studies, it is an ever present complicating factor. Smooth muscle tone will massively affect not only existing geometrical appearance (lumen size and wall thickness), but will modify elastic properties, affect tissue homogeneity and, as we will see yield a substantial part of tissue viscosity. For this reason, biomechanical measurements should be made either in vivo or under in vitro conditions that mimic the in vivo situation in composition of the tissue bath in which the vascular tissue is tested. The vascular smooth muscle tone should be set to supposed in vivo values, or, the measurements should be made at different levels of smooth muscle tone. Unfortunately, the smooth muscle tone itself does change in response to distending forces (myogenic response) or to endothelial shear of flow (endothelial dilation). For many non-living material the stress-strain characteristics will be conveniently linear at least in a certain segment of the curve. That allows the definition of a single elastic modulus to characterize elasticity. Rigidity of vascular walls, however, always heavily depends on actual values of wall stress, the higher is the stress, the steeper will be the stress-strain characteristic curve, providing higher values of their locally computed ratio (tangent), the incremental elastic modulus. Attempts to find a simple description how the elastic modulus of the vessel wall changes with stress failed until now. Hopes that the elastic modulus linearly changes with stress (an exponential shape for the stress-strain relationship) did not bear the critics of more accurate measurements. According to our

experience, a double-exponential approach yields almost satisfactory results (Orosz 1999a, 1999b).

4. Network and branching geometry

We must not forget that hemodynamics will be determined at least as much by network properties of the whole networks than by properties of individual vascular segments. However, networks lend themselves to study and analysis with much more difficulty, both methodical and computational, than do individual segments. For this reason network properties are much less analyzed in the literature. For want of space we will refrain from a more detailed analysis of the effect of mechanical factors on the development of the network properties. Network developments seem to follow the law of minimum energy requirement (Rossitti 1963). That can be altered in aging networks and at chronically elevated pressure (Nadasy 2000, Lorant 2003). A well analyzed territory is the retinal arteriolar network. Rarefaction, that is, the decreased number of parallelly connected resistance arteries seems to be an important contributor to morphologically elevated vascular resistance in chronic hypertension (Harper 1978). The "chaos theory" seems to be one fruitful approach to describe general laws of geometric vascular network development (Herman 2001).

5. Segmental geometry

5.1 Optimal cylindrical symmetry

Most vessels, especially arteries are smooth lined, long cylindrical tubes, positioned in-between larger branchings (Schwartz 1980). This shape is optimal to ensure minimum loss of hydrodynamic energy provided by heart contractions and homogenous distribution of force around the circumference and along the axis, produced by intraluminal pressure. In real situations, however, especially in pathologic ones, deviations from this optimum do occur, in the axial, circumferential and radial directions.

5.2 Disturbances of axial symmetry

To reach their anatomical targets vessels should bend, but that *axial bending* is usually kept to a minimum by adjusting the axis to an arched curve with a large radius. Anatomical situation, however, can force the course of a vessel axis into a narrow bend. The typical anatomical pattern of the large artery system of mammals with the aortic arch itself forms a narrow bending for a very large mass of flowing blood. A sensitive area in human vascular anatomy is the base of the skull, here the inner carotid artery is forced into a narrow, S shaped bony channel, the carotid siphon. Arteries passing joints should follow the position of the joint. In mammalian embryology, a frequent situation is that vessels originally developing as branches deviating in an angle from mother vessel will enlarge their lumen and taking over the role of the distal main branch, which itself then regresses. The originally sharp angle of the axis in such cases will be later splayed to an arch as a rule. Somewhat similar situation can be observed in adult pathology, when developing collaterals bypass the site of slowly developing vascular stricture. Adjustment of the course of the axis is not as effective in such cases, and a broken course of an artery will be a frequent observation on X-ray angiography (coronary, leg). *Irregular course* is a frequent pathological feature in resistance arteries, too. It can be observed in retinal arteries in hypertension and in aging

and is one of the main symptoms of the venous varicosity disease. One current explanation for pathomechanism of varicose notches is that as pressure-induced axial elongation will not be counteracted by sufficient axial prestretch and tether, the vessel axis bends first, then with increasing instability it irreversibly buckles into one direction.

Axial irregularities of lumen diameter and wall thickness are the very essence of vascular pathology. In fact other irregularities of lumen shape will frequently go on unnoticed until the events will develop toward local narrowing, disturbing flow or induce local distension, aneurysm, compressing neighboring tissues or endangering with imminent rupture and bleeding. However, there is a physiological disturbance of cylindrical symmetry at side branches of arteries. An endothelial cushion just over the orifice ensures that axial blood rich in red blood cells will be diverted into the side branch, preventing thus plasma skimming. *Focal pathologic processes* typical for arteriosclerosis will typically disturb cylindrical symmetries in all directions. On the other hand, such focal lesions in turn typically develop where bends, angles, side branches, strictures by impressions of surrounding tissues disturb cylindrical symmetry of vessel shape and laminar flow. Uneven lumen and wall thickness along the axis in many resistance arteries is almost the definition of the diabetic microangiopathy. This causes tissue flow disturbance and microaneurysms endangering with rupture.

5.3 Circumferential deviations from cylindrical symmetry

Slight circumferential deviations from cylindrical symmetry are inherent in case of vessels running on bony surfaces. Careful analysis shows that the thoracic and abdominal arteries are not fully circular, but of an ovoid shape with a somewhat wider base from which the intercostal and lumbar arteries emerge. Ellipticity of lumen cross section has been thought to be the very essence of venous mechanics. And really, certain veins, e. g. the lumen of human inner jugular vein forms but a narrow slit at low pressures, which is for this vessel, in the erect body position. Other veins, however, are surprisingly circular even at fairly low pressures. Not much deviation of the anteroposterior and mediolateral diameters of the human brachial and axial veins could be observed by in vivo ultrasonographic measurements in a wide pressure range (Berczi 2005). While increasing ellipticity is characteristic for cannulated venous segments in the low pressure range in vitro, in vivo, or even in situ, such collapse of one of the diameters is restricted by the radial tethering provided by surrounding fat and fascial tissue down to 0 mmHg transmural pressure (Nadasy unpublished). Disturbances of circumferential symmetry, however are occurring as a rule in case of focal atherosclerotic lesions and in any case of mural thrombosis. Present techniques at hand can analyze the differences of histologic composition around the vessel circumference (and in the wall along the radius), but the biomechanical consequences, uneven distribution of force on force bearing elements, are still poorly understood. We are convinced, however, that it is a key issue in the pathomechanism of the progressive development of the arteriosclerotic plaque. With destruction of the inner media in a sector of the wall, large pulsatile forces will be transmitted to the outer layers in this segment, with the consequence of accumulation of collagenous fibers and cessation of vasa vasorum flow. While some remodeling of the force-bearing elements of the wall can make revascularization possible, a necrotic nucleus, getting closer to the luminal surface and endangering with rupture into the vascular lumen, will be the most dangerous threat caused by the focal process. Some modern techniques raise the hope that distribution of force inside the vessel

wall could be once directly studied. Greenwald has directly demonstrated the sequential strengthening of connective tissue elements (Greenwald 2007).

5.4 Radial asymmetry

Concerning the *radial asymmetry*, original views that a rigid adventitia could prevent further distention of the elastic media ("an elastic ball in a string bag" model), still vivid in the views of non-specialists has been opposed by direct elastic measurements on vessels from which the adventitia has been removed. Right now it seems that the adventitia, with its mostly loose connective tissue, is the site more for the axial tether, than for any contribution to circumferential force-bearing. Vasa vasorum, sympathetic nerves can run in it undisturbed by tissue pressure, the fibroblasts in it with their ability to differentiate into vascular smooth muscle cells can ensure an "appositional" medial thickening. There is an inherent, physiological radial inhomogeneity of the media itself in the wall of large arteries, circumferential elastic sheets (whith holes in them) and smooth muscle cells packed in angle with radius in a fish-bone pattern are forming alternative layers. Taking into consideration that intraluminal pressures at the inner surface should be decreased down to zero at the outer surface, it is really surprising to observe, still how similar are these layers and their elastic and smooth muscle components. This supports, unproven yet views that some equalization process in the media should exist, that distributes the large circumferential force to the similar wall constituents in a similar manner. Some radial inhomogeneity of force distribution, however, should exist in the wall. This can be proven by the elegant experiments of just cutting up vessel rings in the radial directions. The ring will be opened, the angle of which in such a state of zero stress can be measured and analyzed (Liu 1988). We must not forget, however, that the artery wall is never at zero at stress in vivo, fiber arrangement adapted to real pressurized wall tensions. In case of larger vessels the contribution of the endothelium to elastic properties of the wall is thought to be negligible. However, the basal membrane of the capillary vessels lends sufficient rigidity and tensile strength to these vessels. In addition, intimal thickenings of sclerotized vessels can take up a substantial part of wall stress, relieving thus the outer layer of the affected segments.

5.5 Vascular diameter

Vascular specialists with biomechanical backgrounds are rarely satisfied when "the" diameter of a vessel is mentioned. All vessels alter their diameter as a result of acute smooth muscle contraction, and the same measured intraluminal diameter could mean very different vessels at different levels of vascular smooth muscle tone (a larger vessel but with a larger tone), and different measured intraluminal diameters could mean a morphologically identical vessel segment but with a somewhat altered tone. The diapason between maximum and minimum contractions is routinely measured now in wire and pressure angiography, and such practice is more and more frequently applied in in vivo measurements and to some degree, even in clinical practice.

For the exact biomechanical analysis, we have to discriminate between the morphological diameter of the segment, best characterized by its fully relaxed state, its diameter in full contraction, which in healthy arteries below about 1 mm of inner diameter will be the fully closed segment, and the actual diameter measured in a discrete state at a given level of

muscle tone. Things will be even more complicated when we realize that vascular lumen will also be dependent on transmural pressure, elasticity of the wall and also even on axial distension. Fortunately, relaxed vessels pressurized close to or somewhat over physiological pressures, turn to fairly rigid structures and do not further change much their lumina as a function of pressure. This stable diameter will well characterize the morphological lumen. In the scientific practice it is even more accurate to characterize morphological lumen with the whole course of the relaxed pressure-diameter curve.

5.6 Physiological control of the morphological lumen

The "passive" (morphological) lumen will be differently controlled and with more delay than the actual lumen is determined by the actual level of smooth muscle tone. The morphological control process needs a reorganization of the histological components of the wall. The terms "*remodeling*" (segmental remodeling, geometrical remodeling, wall remodeling) or "*long term control*" are used to describe it (Fig.2.and 3.).

It had been known for ages that vessels with larger flows have larger lumina. The problem can be reduced to the question, that branching of a larger mother vessel how will effect the lumens of the smaller and smaller daughter branches? Early analysis of pressure and flow in vascular networks have shown that while mean linear velocities are decreasing toward smaller branches (30 cm/sec in the aorta, a few hundred micrometers in the capillaries) there is an elevation of mean pressure drop per unit length. There is hardly any drop in mean arterial pressure in large arteries, substantial pressure drop occurs along a few cm length of small arteries with a few hundred μm of diameter, finally, a sharp drop of pressure happens in arterioles, a few mm of lengths, but with diameters between 30-150 μm. (Abramson 1962, Cliff 1976, Milnor 1982, Schwartz 1980). In the simplest case of symmetric branching, to maintain the mean linear velocity in daughter branches would need a ratio of radii of daughter (r_d) to mother (r_m) branches of $\Pi r_d^2 + \Pi r_d^2 = \Pi r_m^2$; from whence $2\, r_d^2 = r_m^2$ and $r_d / r_m = 1/\sqrt{2} = 0.707$. To maintain the unit pressure drop per unit length (with unaltered viscosity, following the Hagen-Poisseuille law) would need daughter to mother radius ratios of $Q = \Pi/8 * r_m^4/\eta * \Delta p/\Delta l = 2 * \Pi/8 * r_d^4/\eta * \Delta p/\Delta l$; from whence $2\, r_d^4 = r_m^4$ and $r_d / r_m = 1/\sqrt[4]{2} = 0.841$. Hemodynamic analysis of existing arterial networks thus leads us to the conclusion, that in case of symmetrical branching daughter to mother branch ratios should be in-between these two values, m $0.707 < r_d / r_m < 0.841$. Measuring many arterial diameters Murray has suggested, that in case of any types of branchings, the equation of $r_m^3 = r_{d1}^3 + r_{d2}^3 + r_{d3}^3 + r_{d4}^3 + \ldots$ will be valid. This seems a fairly good approach even in our days. How the vessel wall should "know" how much is the flow in its lumen? The answer was given in two classic works by the great American cardiologist, Rodbard, who supposed that endothelial shear is somehow sensed by the endothelial cells and is kept constant by chronic morphogenetic processes adjusting vascular lumen to flow. The value of endothelial shear rate (dv/dr) computed based on the Hagen-Poiseuille law is $dv/dr = 4Q/\Pi r^3$ (where Q is the volume flow and r is the inner radius) being in accordance with Murrays law. For our symmetric bifurcation, $dv_d/dr_d = dv_m/dr_m$ and $4(Q/2)/\Pi r_d^3 = 4Q/\Pi r_m^3$ from whence $2\, r_d^3 = r_m^3$ (the form corresponding to Murray's law) and finally, $r_d / r_m = 1/\sqrt[3]{2} = 0.794$. This latter number is just in-between 0.707 and 0.841 as required by common hemodynamic experience. Validity of such computations has been proven in analysis of several types of vascular branchings (Lorant 2003, Nadasy 1981, Pries 2005, Rodbard 1970, 1975, Zamir 1977).

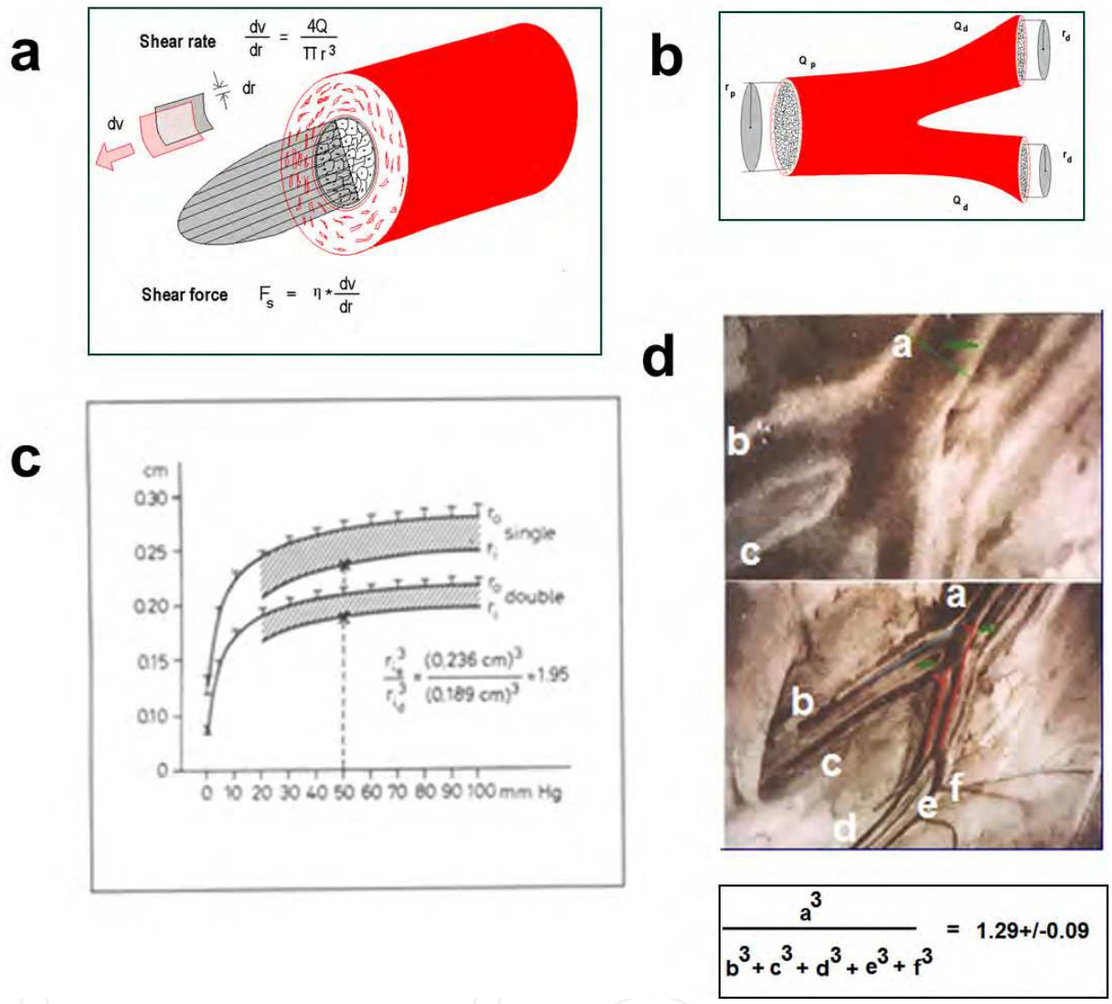

Fig. 2. Morphological (long-term) control of vascular lumen. a. Shear rate and shear stress in a cylindrical vessel with continuous flow. b. Geometry of a symmetric branching. c. Relevance of the Murray-Rodbard law: Pressure diameter plots of normal double and single (morphologically malformed) human umbilical artery segments. The ratio of the cubes of inner radii at physiological pressures is around, 2 which can be expected in case of doubled flow in single arteries. (From Nadasy 1981, with permission of Karger) c. Relevance of the Murray-Rodbard law: In vivo microprepared popliteal confluence of the rat saphenous vein. Video-microscopic records at two magnifications with normal pressure and flow in the lumen of anesthetized animals. The ratio of the cube of diameter of the mother branch to the sum of cubes of diameters of daughter branches is close to the expected 1 (from Lorant 2003, with permission of Physiol Res, Czech Academy of Sciences).

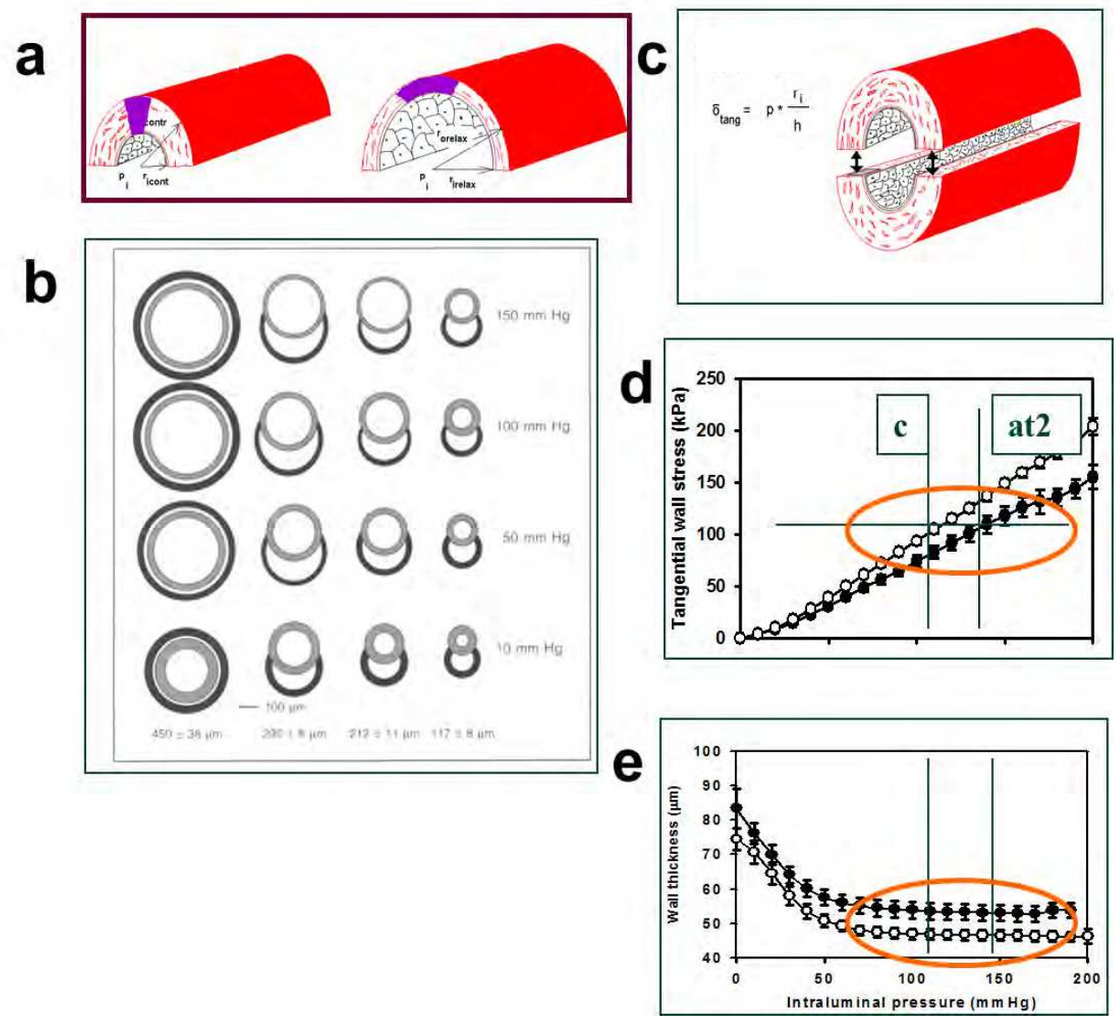

Fig. 3. Long-term control of vascular wall thickness. a. Vessels with thicker walls can more effectively control their inner diameter, a feature characteristic for resistance arteries. b. Series of intramural coronary resistance arteries from the rat. Contours of cross sections are shown. From left to right, morphologically different segments with diameters around 4-500, 300, 200 and 100 micrometers. From up to down, at different transmural pressures. Passive and contracted segments are shown. Note typical increasing thickness-to-diameter ratio toward smaller arteries, increasing effectivity of lumen control. (From Szekeres 1998, with permission of Karger) c. Parameters determining tangential wall stress. d and e. Wall stress and wall thickness of a resistance sized small artery from normotensive and hypertensive animals. Note that elevation of wall thickness (and reduction of lumen) just ensured unaltered wall stresses at elevated in vivo pressures as could be expected by the Folkow-Rodbard-Mulvany law (from Nadasy 2010, with permission of Karger).

At a more scrutinizing analysis, however, the situation will be more complicated than that. In fact, not shear rates but shear forces will be sensed. This latter will be the function of blood viscosity, a fairly elusive factor supposing its dependence on shear stress (the blood being a non-Newtonian fluid) and on the level of accumulation of red blood cells in the axial

flow (according to the Fahreus-Lindquist law). At a fairly good flow, and especially in smaller vessels, almost clear plasma, devoid of cellular elements will slide along the luminal surfaces of endothelial cells, yielding a fairly continuous viscosity of 2-3 cP. The other problem is the changing levels of flow (depending on pressure and on more distal resistance) and changing levels of arterial tone. Based on experience on skeletal muscle circulation, we have to suppose that relative short periods with high flows will be sufficient stimuli to increase the morphological lumen. On the contrary, when maximum flows do not come for a while, shortened circumferences could get morphologically stabilized reducing the range of luminal vascular smooth muscle control (Nadasy 2010a). An other problem will be prominent when we compare arteries and veins. Mean velocity of blood flow is about half as fast as in corresponding arteries. We have to suppose that either other factors than blood flow contribute substantially to morphological lumen control in veins or, the venous endothelium is differently tuned to flow sensation than is the arterial. To solve these questions would be essential to reveal the pathomechanism of chronic venous diseases. An other complication is rising from wall thickness adjustment to elevated pressure, which, can reduce lumen below levels required by flow inducing thus resistance elevation and having a stabilizing effect on the high blood pressure. Which is the cause and which is the effect? Fine network analyses in different states of circulation and in different stages of the hypertension disease will be needed fully to describe the intermingling feedback networks of flow, resistance and pressure. We believe that a disturbed endothelium will not be sufficient to restore morphological lumen to rare flow maxima, or to counteract the lumen-narrowing effects of adaptive wall thickening. Extensive studies revealed a set of cytophysiologic and even molecular mechanisms how shear is sensed at endothelial luminal surfaces.

Summing up this chapter, we have to conclude that despite many remaining questions, the law, describing the long term morphological control of vascular lumen formation, originally found by Murray and by Rodbard (1970, 1975) has proven its validity for a substantial period of time (Kamiya 1980, Lorant 2003) and can be accepted as one basal law of normal vascular functioning. It can now stated with a high level of certainty that long term control processes in the vascular wall do exist that adjust morphological lumen to flow so that they tend to stabilize endothelial shear.

5.7 Physiological control of vessel wall thickness

Vessels with higher pressures have thicker walls. The pulmonary arteries have thicker walls than the caval veins and the aorta than the pulmonary trunk, despite similar flows. Higher pressure means higher tangential force per unit length (F) on vessel circumference, $F= p*r_i$, where p is the transmural pressure and r_i is the inner radius (Fig.3.). That can be distributed on a vessel wall thickness of h, $\sigma = p*r_i / h$, where σ is the tangential stress. Folkow observed that arterial wall thickness increases in a compensatory manner in hypertension (1971, 1990, 1995). An other assumption published by Rodbard (1975) stated that morphological thickness of the vascular wall is controlled to stabilize the value of tangential stress. But there are more problems with this observation. As there is hardly any drop in mean arterial pressure along Windkessel and distributing arteries (to about 600 μm of inner diameter) inner radius to wall thickness ratios should have remained unaltered along the whole arterial tree to make σ unaltered, too. In fact radius to wall thickness ratios decrease toward smaller arteries. What is even more contradicting, in more distal resistance arteries

following a substantial pressure drop, radius to wall thickness ratios should increase to compensate for lower pressures to ensure stable values of tangential stress. Just the opposite is the case: small resistance arteries have relative thicker walls, and computed in vivo values for tangential stress decrease along the arterial tree reaching very low values in smallest resistance arteries. First we have to see what is the advantage of such a difference (Fig. 3a). Smooth muscle in large vessels will not contract to induce substantial reduction in diameter. That would be useless, as no substantial pressure drop could be reached taking into consideration real flow and viscosity values. But there is an opposite situation at the level of the resistance arteries: fast and effective acute changes in lumen are the very essence of their physiological functioning. Contraction of a helical smooth muscle cell ring at the outer surface of a resistance artery wall will be much more effective than the contraction at the inner site of the wall, the difference will be the higher the thicker the resistance artery wall is. A 20 % contraction at the inner circumference will induce 20% reduction of the lumen (2.4fold increase in segmental resistance). A similar 20% contraction at the outer circumference will induce 32.9, 47.0 and 100% reduction in lumen in vessels with 10:1, 8:1 and 6:1 radius to wall thickness ratios, respectively as they will push the inner vascular wall layers into the lumen. This will result respective segmental resistance elevations of 4.9 and 12.7 times in the first and second cases, while the lumen will be fully closed and flow will cease in the third situation. The question, however, can be raised, that as tangential stresses are so much less in smaller arteries, are the smooth muscle cells themselves in this vessels so much different? Several differences between smooth muscles of these vessels could be listed, but one outstanding difference is the presence and amount of elastic tissue which is diminishing toward the peripheral arteries practically synchronously with the reduction of the r_i/h ratio. A simple solution can be that while smooth muscle is similarly stressed in large and small arteries, the parallelly connected elastic membranes will bear a substantial part of the tangential strain. But later we will see that amount of elastic tissue will develop in response to pulsatile not steady stress. And we will also see that elastic tissue has also its impact in the lower part (below diastolic pressures) of the arterial pressure-diameter characteristics. And with that restriction the Folkow- Rodbard-Mulvany's law on long term control of the thickness of the vascular wall can now be valid (Rodbard 1970, 1975*): Vessel wall thickness develops to stabilize tangential wall stress – valid, when tissue composition is unaltered.*

Thickened wall of affected vessels is a main alteration in case of chronic arterial hypertension (Folkow 1971, 1990, 1995), chronic pulmonary hypertension and venous pressure elevation in chronic venous disease. In several clinical and experimental studies, hypertensive remodeling of arteries seemed just to stabilize in vivo tangential wall stress. Such control mechanisms should exist at least in a certain phase of the hypertension disease (Albinsson 2004, Dickhout 2000, Frisbee 1999, Hayashi 2009, Nadasy 2010a, Pries 2005).

6. Vascular elasticity

6.1 Significance of vascular elasticity

As we could see above, elasticity is a very important, inherent property of blood vessels, it ensures the fairly continuous pressure and flow in small vessels despite periodic functioning of the heart pump (Bergel 1961, 1964, Fung 1984, Gow 1972). Actual geometric properties of a vessel, determining their hydrodynamic resistance are in turn determined by their

morphological geometry, the actual level of smooth muscle tone, transmural pressure, luminal flow inducing endothelial dilation, their axial stretch and the elasticity of the wall. The role of elasticity in forming the actual geometry will be more important in vessels with high distensibility, where small changes in transmural pressure will induce large changes in lumen volume in such vessels. As we will see later, most vessels are relative rigid at and especially above physiological pressures. That means that elasticity will be a central parameter in determining lumen size when pressures in the lumen decrease below physiological pressures. We have a good reason to think that elasticity of force-bearing fibers in the vascular wall helps to maintain a fairly even distribution of distending forces and stretches among parallelly and serially stressed wall components: elongation of a stressed fiber transfers part of the force onto the parallelly connected poorly stressed fibers. More elongation in the less stressed serially connected fibers will help an even distribution of stretch among the serially connected circumferential elements of the wall. One central problem in vascular pathology, we believe, is the elastic force-bearing capacity of the inner layers of larger vessels: by their force-bearing they relieve the outer layers. Decreasing hydrostatic pressures in the outer layers of the vessel wall make possible the proper functioning of the vasa vasorum and proper nourishment of the whole wall.

6.2 Parameters measuring elasticity

We can determine the elasticity of a vascular segment *in vivo* directly, by measuring geometrical parameters (inner, outer diameter, wall thickness) at different levels of pressure (Fung 1984). Modern *ultrasonography* (from the surface of the body and also intravascular) provides sufficient means for larger vessels (Berczi 2005, Molnar 2006, Mersich 2005, Shimazu 1986). A certain level of manipulation of pressure and smooth muscle tone is possible even in human volunteers (See Fig. 1c.). In vivo animal experiments of course give a wider and more accurate potential for that. Delicate measurements can be made on isolated, axially isometric, cylindrical vascular segments mounted in the tissue bath of a *pressure angiometer* (Cox 1974, Duling 1981, Nadasy 2001, see 1b.). The pressure-diameter characteristics can be recorded at different levels of smooth muscle contraction (with vasoconstrictors added) and in the so called passive state (fully relaxed smooth muscle e.g. with calcium-free incubation medium). We can cut rings, circular or helical strips and study them in a *wire myograph* (Fig. 1a.). To characterize circumferential (tangential) elasticity we can compute *compliance*, $C=\Delta V/\Delta p$, that is volume alteration in response to unit alteration in (transmural) pressure. The question, answered by the compliance value is, that how much the pressure will change if we press a certain amount of blood into the vessel. This parameter is frequently used to characterize venous elasticity and even for large arteries. One problem with it is, that a rigid, large vessel will have larger compliance than a small elastic one. To circumvent this problem the term *distensibility* has been applied, simply normalizing volume change to the initial volume (V_o), $D=\Delta V/ V_o *(1/\Delta p)$. Distensibility almost fully describes the elastic properties of the wall, the way it is taking part in hydrodynamic processes, and is used frequently in hydrodynamic models for this reason. However, it will not properly characterize the elasticity of the wall material as more elastic, but thicker walls can have the same distensibility. The Young's *elastic modulus* will be computed, which is the tangent of the stress-strain relationship. For cylindrical segments with inner and outer radii of r_i and r_o, respectively, with not negligible, but relative thin walls (valid for most vessels) the equation given by RH Cox (1974, 1975a, 1975b), the

inventor of pressure angiometer (Fig. 1b.) is mostly accepted: $E= 2r_o r_i^2/ (r_o^2 - r_i^2)*(\Delta p/\Delta r_o)$, where Δp is the pressure change inducing an alteration of the outer radius, Δr_o. As we described it earlier, elasticity of the vascular wall will be heavily dependent on the conditions under which we have measured it. For this reason, we have to repeat the measurements at different levels of wall stress (intraluminal pressure) and at different levels of smooth muscle tone. Typically, pressure-diameter characteristics will be recorded at different levels of smooth muscle tone. If pressure alterations are slow enough, we can suppose that the wall is transiting a series of equilibrium states and each further infinitesimal elevation in pressure (stress) will induce an infinitesimal rise in circumference (strain) and the tangent of the normalized pressure-volume curve (incremental distensibility) and tangent of the stress-strain curve (incremental elastic modulus) can be computed and plotted as a function of pressure ("isobaric" parameters). Or, in case of the incremental elastic modulus, it will frequently be given as a function of computed wall stress. Such elastic modulus-tangential stress characteristics will characterize best the elasticity of the wall material itself. The vertical axis is usually logarithmic, but will not be linear even in this form. The question here can be raised how reproducible and how characteristic for the in vivo situation the elastic parameters measured this way will be? One problem is the different levels of smooth muscle tone. That has to be somehow stabilized, which is not so easy as it itself changes with changing wall stress. In case of a well developed myogenic response, as it is the case with many resistance arteries, elevated pressures will not produce elastic dilation but myogenic contraction (Kuo 1988, Osol 1985, Szekeres 2004). The term plasticity is used for a typical behavior pattern of vascular smooth muscle: the material of the wall somehow adapts to lasting pressure loads or pressure patterns. The mechanical past of the vessel (in the last few minutes) determines to some degree its present mechanical behavior.

For this reason, reproducibility should be ensured by preliminary incubation of the segment under controlled contractile and mechanical conditions (continuous or cyclic stress or pressure load). Stress or pressure changes during elastic measurements should be applied following a reproducible pattern: rises at continuous rates, stepwise rises, cyclic sinusoid or triangle patterns are widely used. Because of viscosity, characteristics taken with increasing and decreasing loads might differ. Elastic moduli in the range of 10^4 Pa can be considered as very low, found only at very low wall stresses, at a few mmHg intraluminal pressure in arteries, and close to 0 mmHg pressure in veins. Values of 10^6 Pa (10^5-10^7) are typical for many vessels in their physiological pressure range. Further elevating the pressure values in the lumen 10^7 Pa can be reached with any type of vessels (veins included!), but a damage to the wall (mostly reflected by reduced smooth muscle contractility) is in such cases imminent. The tensile strength of healthy vessels is surprisingly high, veins can be sutured as bypasses into the arterial system and arteries will endure for a shorter period 1 atmospheric transmural pressure. Tangential stresses in vivo range from the very low values of a few 10^4 Pa (e.g. 30 mmHg = 4 kPA pressure, r_i/h values around 3, for a thick walled, contracted arteriole, $\sigma= 1.2*10^4$ Pa) to highest measured values (e.g. 150 mmHg=20 kPa elevated systolic pressure for a thin walled large artery with r_i/h ratios around 10, $\sigma= 2*10^5$ Pa). Stresses in the range of 10^6 Pa will damage the wall as maximum forces produced by the smooth muscle are in the range of 3-5 atm (~$3\text{-}5*10^5$ Pa, 200-400 mmHg for a large vessel with a radius to thickness ratio of 10).

In in vivo experiments and in the clinical practice, too, vascular elasticity is frequently measured indirectly. The shape of the aortic pressure curve can be analyzed. The so called

augmentation index gives an indirect information about the rigidity of the large arteries. Even more popular is the determination of the pulse wave velocity. These will be discussed in more detail in the chapter on the Windkessel arteries.

6.3 Effect of histological composition on vascular elasticity

After several decades of systemic investigations now we have a fairly good if not final picture how the histological composition of the vascular wall affects its elasticity (Apter 1966, Bergel 1961, 1964, Cox 1975a, 1978, Dobrin 1978, Fung 1984, 1995, Gow 1972, Greenwald 2007, Koens 2010, Oxlund 1986, Roach 1957, VanDijk 1984, Vidik 1982). The endothelium will not much contribute to the mechanical properties with the exception of capillaries and maybe, of the smallest other vessels. But we must not forget, that it is the endothelium that senses the shear at the inner surface of vessels and adjusts the diameter to it (see endothelial dilation, and vascular lumen control). Also, the endothelium, with the basement membrane underneath it, is a fairly mechanically stable structure forming the capillary walls. Capillaries in the renal glomeruli seem to be enforced by the leg processes of the podocytes there. Contrary to earlier expectations, the loose connective tissue of the adventitia will not restrict pressure-induced dilation of an elastic media ("elastic balloon in a string bag" model, Burton 1954). The collagenous fibers running in it will ensure some axial tether when, with decreasing pressures the axial extension of the arteries decreases. In case of veins at very low pressures, and in arteries at extremely large levels of medial smooth muscle contraction, we can suppose even some adventitial radial tether. Vascular smooth muscle if relaxed does not resist distending force until the intracellular fiber structure is not stretched. Vascular structures containing abundant smooth muscle (umbilical artery, resistance arteries) have very low elastic moduli at low stresses and high moduli at high stresses. At least part of the elasticity of the stretched vascular smooth muscle will be determined by elasticity in the actomyosin crossbridges ("series elasticity", Mulvany 1981, Siegman 1976), and should reflect the mechanical deformation of the myosin head or neck in response to distending forces. In fact, as each smooth muscle cell is surrounded by a socket of basal lamina, composed of collagenous fibers, and there is an intracellular scaffold in them formed of intermediate filaments and dense bodies, and to go further, bundles of actin filaments are more abundant in them than thick myosin filaments, contribution of these latter structures to "Series elasticity" cannot be excluded. We have found that elasticity of vascular tissue, rich in smooth muscle can be explained as originating from a "unit elasticity", possibly the elasticity of the actin filaments. Upon cyclic loading, the number of serially and parallely connected elastic units could adapt by breaking up and passive slide of overstressed latching actomyosin crossbridges as well as by spontaneous shortening in understressed ones. That ensured uniform stretch and load in affected filamentous units (Nadasy 1987, 2007b, Szekeres 1998).

Collagen lends rigidity and high tensile strength to the vascular wall, again, at high distending forces, while very moderate forces are sufficient to strengthen the coiled up collagenous bundles in the vessel wall. More collagen in the wall usually means higher rigidity (Apter 1966, Bergel 1961, 1964, Cox 1978, Dobrin 1978, Gow 1972, Greenwald 2007, Hegedus 1984, Oxlund 1986, Vidik 1982), but usually only at higher stresses. Collagen accumulation is typical in many types of diseased vessels ("sick vessel syndrome", Heistad 1995). Contrary to the other two wall constituents, *elastin* will resist distension even at very low stretches but will not be fully stretched even at high distending forces. The result is that

its presence elevates elastic modulus (increases rigidity!) at low pressures, but decreases it at high tangential forces (Fig. 4b.). Frequent contradictions about connective tissue composition and measured elastic modulus can be prevented by exact analysis of the pressure and tangential stress levels where the measurements have been made. Plots of tangential elastic modulus against tangential stress usually are in good accordance with histological composition. Such plots are accepted as reflecting the elastic properties of the wall material itself. Still it is poorly understood how the elastic laminae are mechanically connected to smooth muscle. In rabbit aortic strips we have found that series and parallel elastic components of this elastic tissue changed parallelly upon passive stretch (Nadasy 2007b). But similar observations were made in the aneurysmic tissue fully devoid of muscle and elastic components (Toth 1998).

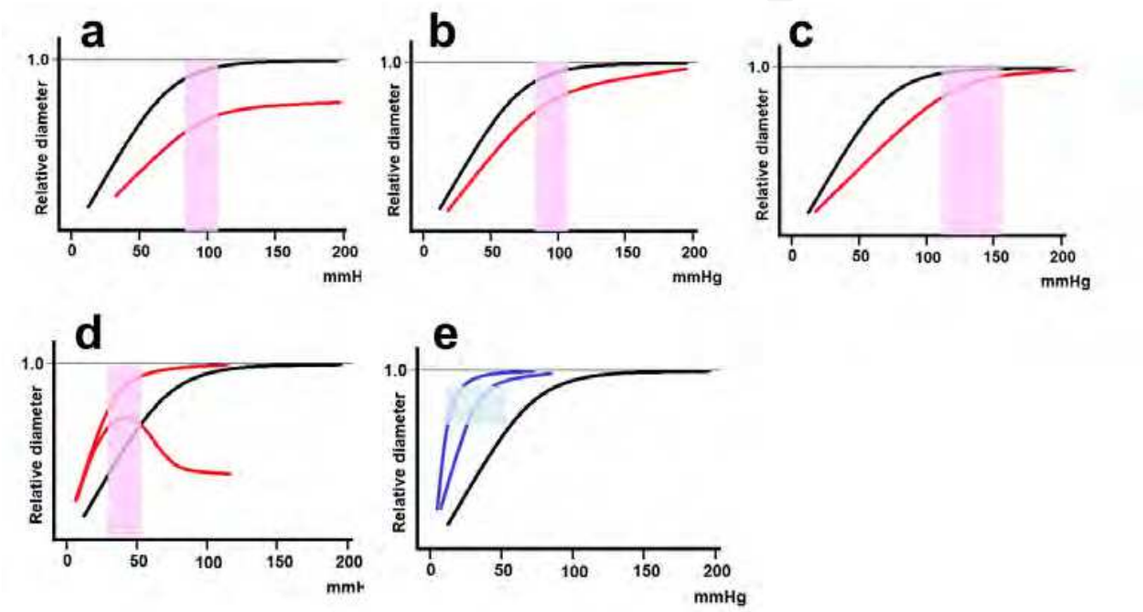

Fig. 4. Long and short term control of vascular elasticity. Comparisons of pressure-diameter characteristics of different vessels. Relative values of diameter are shown. Black lines represent the characteristics of a typical distributing artery in the relaxed state (same in each diagram). Shaded areas mark the range of in vivo pressures of vessels being compared (drawn in color) a. Red, the same artery in the contracted state. Smooth muscle contraction reduces elastic modulus as a function of pressure but increases it as a function of strain. (Cox-Dobrin law) b. Comparison with a more elastic (Windkessel) artery (red). Note decreased distensibility at low pressures and increased distensibility at high pressures c. Comparison with a hypertensively remodeled artery (red). Note upward dislocation (toward elevated in vivo pressures) of the transition between more and less distensible parts of the characteristic curve. d. Comparison with a resistance artery in the relaxed and contracted state (red). Note transition between more and less distensible parts of the characteristic curve toward lower pressures existing in vivo in these more distal resistance vessels. e. Comparison with elasticity of upper body (left, blue) and leg (right, blue) veins. Transition between more and less distensible parts of the pressure diameter characteristic curves also corresponds to in vivo occurring pressures in these vessels (Burton-Roach-Kadar law).

6.4 Typical shape of the vascular elasticity curve

As a result of the elastic properties of their components, *all vessels, without exception show, elastic characteristics with relative similar shapes* (Burton 1954, Dobrin 1978, Roach 1957, Wolinsky 1967, Fig. 4.). Their elastic modulus increases with stress in a such a manner that *they are distensible at lower than commonly occurring physiological pressures and turn rigid at higher pressures* (Burton-Roach-Kadar law). (Berczi 2005, Busse 1981, Cox 1975b, Gow 1972, Molnar A 2006. Molnar G 2010, Roach 1957, Stooker 2003, Szentivanyi 1998) The physiological working point of the vessel is somewhere at the turn of the pressure radius characteristic curve. The work-points, of course will be different for aortas, small resistance vessels, veins, embryonic vessels and hypertensive vessels (Fig. 4.). But that will hardly affect the validity of the above statement. Such an organization of vascular elasticity can be considered biologically logical: potential rises in pressure will not induce unlimited distension, while unexpected volume reductions will be "followed" by the elastic shrinkage of the wall, stabilizing to some degree against fast pressure drop. Larger smooth muscle tone can cause some complications (see next chapter).

6.5 Control of vascular elasticity

In addition to reduce inner radius (and to increase wall thickness) vascular smooth muscle contraction substantially alters the elastic properties of vessels (Apter 1966, Busse 1981,Cox 1975a, Dobrin 1969, 1978, Gow 1972, Greenwald 1982, Hudetz 1980, Monos 1979, Nadasy 1987, vanDijk 1984, Fig 4a.). In case of large arteries, where the lumen reducing effect practically will not affect flow-resistance, the setting of the elastic modulus can be considered one of the main functions of the smooth muscle in the wall. Effects of smooth muscle contraction on vascular elasticity have been described in some classical publications on vascular mechanics. We can set the rule that *smooth muscle contraction reduces the elastic modulus if plotted against pressure and increases it if plotted against radius* (Cox-Dobrin law) (Busse 1981, Cox 1975a, Dobrin 1969, 1978, Hudetz 1980, Monos 1979). One reason for the reduction of isobaric elastic modulus is the decreased stress (reduced inner radius-elevated wall thickness). The contracted pressure radius curves themselves can be less steep (lower pressures) and more steep (high pressures) than the relaxed ones. Right now we do not have a clear picture how the contractile apparatus of the smooth muscle cells is mechanically connected to the elastic lamina and to the more rigid collagenous components. Contracted pressure radius curves at high level of contraction can be very complicated resisting attempts to describe them as elasticity curves. Segments contracted at low pressures will give a very large hysteresis, that is the difference between the upward and downward routes of the pressure-radius curves will form a large loop. Under in vivo conditions, in arteries, periodic pulsatile pressure gives a "conditioning" effect, that reduces but does not diminish hysteresis. This effect can be mimicked in vitro by repeated pressure-radius cycles. In vessels with a pronounced myogenic effect (resistance arteries) elevating pressure will be responded by active myogenic contraction (Bayliss 1902, Jackson 1989, Kuo 1988, Szekeres 2004).

There is also a long-term control of vascular elasticity. Connective tissue components of the wall can be degraded and rebuilt, their amount can change with altering hemodynamic conditions and pathology (Arribas 1999, Briones 2003, Cox 1988, Greenwald 2007, Vidik 1982). Such alterations are very typical for segmental vascular remodeling processes, and of

course, they will also affect the elastic properties of the vessels. As a rule we can state that such mechanically driven remodeling processes will ensure, with the exceptions of extreme pathologies, just that the shape of the pressure-radius curves will be adjusted to in vivo pressures as described above. The sole cellular component of the media is the vascular smooth muscle cell. In answer to different biomechanical and biochemical stimuli such cells will be transferred to the secretory state and secrete the components of the extracellular matrix. *Elastin production by them will be stimulated by pulsatile pressure changes* with consequent alterations in the pressure-radius characteristic curve (Kadar 1969). Several pathological processes will stimulate the superfluous production of collagen, increasing the vessel wall's rigidity. We have a good reason to think that this is the lesser harm: the high tensile strength of collagen helps prevent fatal rupture of the vascular wall (Toth 1998).

7. Vascular contractility

With the exception of the capillaries and of such extreme pathological states as late fibrosclerotic plaqes and advanced aneurysms, all vascular walls contain of smooth muscle cells in their media, able to contract. Smooth muscle contraction follows the biophysical laws characteristic for isometric and isotonic contraction of other smooth muscle (Herlihy 1973, Lundholm1966). Smooth muscle cells can contract to about 40% of their fully relaxed length. They are able to produce active shortening up to about 5 kp/cm^2 stress, a value similar to skeletal muscle, which latter is much richer in contractile proteins. The rate of vascular smooth muscle contraction is relative slow, full contractions are reached in a few tens of seconds. Typical are the tonic contractions, but certain vascular muscles also do produce periodic contractions (lymph vessels, portal vein, umbilical vessels?). A typical feature is the *spontaneous contraction*, which is more pronounced in microvessels than in large vessels. The smooth muscle slowly contracts in a medium to which no specific vasoconstrictor agent has been added. This spontaneous contraction is, at least partly responsible for the above mentioned "memory" effect. Vascular specimens should be subjected to a standardized equilibration process, lasting about 20-30 minutes to yield reproductive contractile and biomechanical responses. The explanation is the specific control of vascular smooth muscle contractility ensuring certain level of IC calcium without further stimulation. The other feature is the remaining tone. After contraction, in an in vitro contractility study, when the agonist has been washed off, the original resting level of strain or force will not return. This will be typical at low stresses. There is a temptation to apply larger than physiological stresses to prevent this to occur. The other frequent technical solution is the continuous readjustment of resting tone during the measurement. Because of the spontaneous and resting tones, it is a common requirement nowadays to test the passive length or force after incubation in calcium-free medium with fully to relaxed vascular smooth muscle. Vascular smooth muscles are prone to form "latch" contractions. That means that after some shortening their lengths against moderate stresses, the muscle will be able to resist very high passive stresses not distending at all, or distending only at a very slow rate. A slow cyclization of the actomyosin crossbridges is thought to be in the background of such a behavior (Somlyo 1968). Some new observations raised the possibility of a rearrangement of the cytoskeleton, ensuring such "plastic" behavior. We can also mention here that slow yielding to large stresses after latch-type contraction gives base for the stress-relaxation and creep. That is, latch contraction is responsible for at least part of viscotic behavior of the

vascular wall (see also at viscosity). Modern cellular physiology has proven, that separate from contraction control molecular mechanisms will ensure the dephosphorylation of myosin light chains, terminating the actomyosin crossbridge cycle, which means that contraction and relaxation can be controlled somewhat separately in vascular smooth muscle (Schubert 2008). An other feature, we have to mention is the *myogenic contraction*. Passive stress on vascular muscle, especially from small arteries, will induce its active contraction. Such processes can be observed in vivo and form an important mechanism for tissue perfusion autoregulation.

While large arteries will not change their lumen to affect volume blood flow in a sensible manner, smaller arteries and veins can contract until their lumen fully disappears. The extent of contraction, the vascular "tone" is delicately set at different points of the circulation and in different times. Several ten types of cytoplasma membrane and some cytoplasmic receptors have been identified in vascular muscle affecting vascular contractility. Their amount and the extent of contraction or relaxation induced varies in different vascular territories. Also, thousands of drug molecules have been isolated or synthetized that affect vascular contractility, some of the most frequently used cardiovascular drugs are among them. While earlier it was thought that the amount of receptors is specific for the tissue, now we now that even receptor molecule expression is under physiological control, altered receptor expression and altered receptor sensitivity will form important part of vascular remodeling processes.

8. Viscosity of the vessel wall

For methodical reasons, because it is very difficult to study them under reproducible conditions, vessel wall viscosity is an unduly neglected area. Most authors agree that vessels are not only elastic, but viscoelastic (Apter 1966, Azuma 1971, T Bauer 1982, Bergel 1964, Craiem 2008, Fung 1984, Goto 1966, Greven 1976, Hasegawa 1983, Nadasy 1988, Orosz 1999a, 1999b, Steiger 1989, Toth 1998, Zatzman 1954). Vessels show all the three typical viscotic phenomena, the *creep* (viscotic elongation at continuous stress, Fig 5a.), the *stress relaxation* (decreasing stresses after unit-step elongation, Fig 5b.) and *hysteresis* loops (difference between upward and downward routes of the stress-strain curves, Fig. 5c.).

Viscosity might be essential in distributing the force among parallelly connected components of the wall, dampening sudden force elevations on them, preventing their rupture or overwear. There is an agreement that at least part of vascular viscosity will go on in the smooth muscle cells themselves. Our explanation was that *passive slide between actin and myosin filaments*, with breaking and reestablishment of latching cross-bridges could explain vascular viscosity. Viscous elongation this way could be restored by ATP dependent slow contraction and being reversible (Fig. 5a). In pathologic tissue, devoid of functionable smooth muscle cells, a *slow but inherent viscous dilation of extracellular connective tissue fibers* goes toward the fatal rupture of the wall (Fig 5b). Viscoelasticity of the wall can be modeled with Maxwell or Kelvin models, containing one viscous, one parallelly connected and one serially connected elastic units (Fung 1984, Orosz 1999a 1999b). In case of the simple acellular aneurysmal tissue we have identified a fairly continuous stoichiometric ratio between the three viscoelastic components which, first gives some insight into the molecular organizational principles of vascular viscoelasticity (Toth 1998).

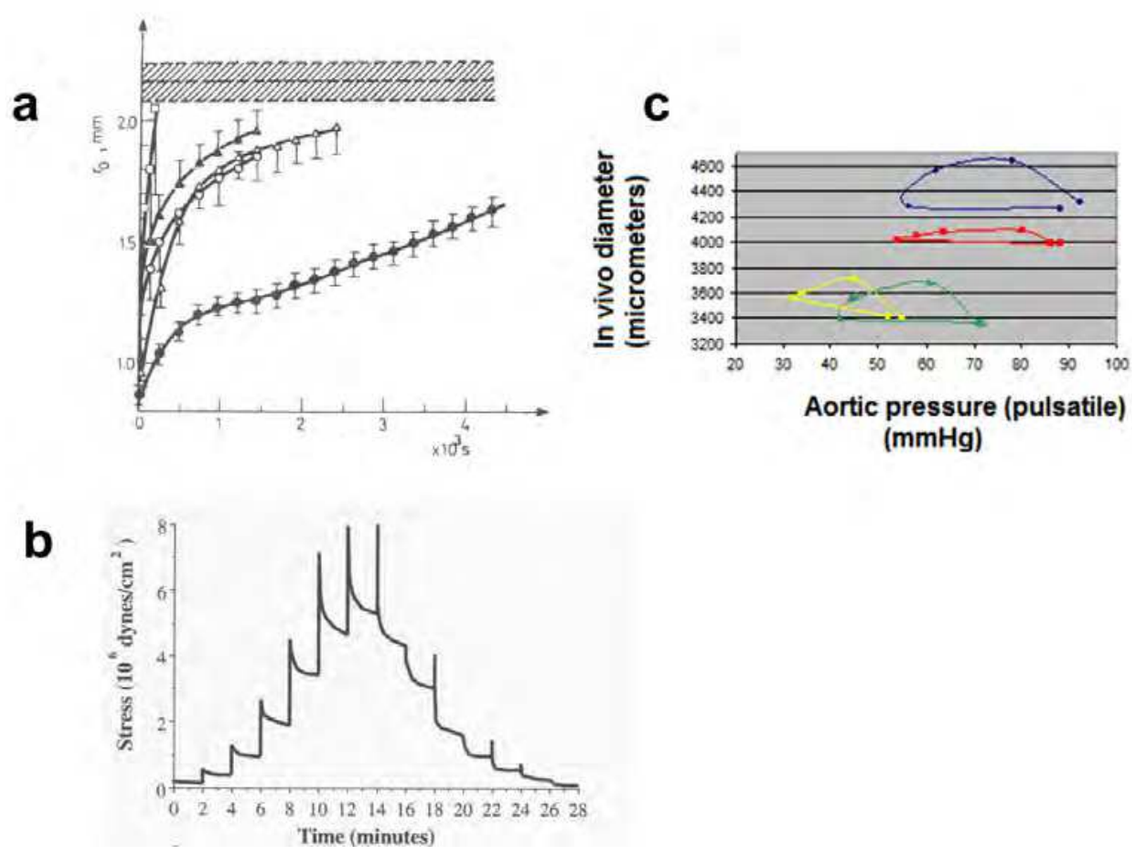

Fig. 5. Blood vessel wall viscosity. a. Viscous creep of contracted human umbilical arterial segments. Slow creep in oxygenized nKR (●), sped up by doubling distending pressure (□), or by applying smooth muscle relaxant, sodium nitrite (○) or with calcium-free solution (▲). Viscosity is also decreased by inhibiting the energy metabolism of smooth muscle cells by 2-deoxy-glucose (Δ). (From Nadasy 1988, with permission of Akadémiai Kiadó) b. Stress relaxation and tensile strength of human aneurysmic tissue. Strip from brain aneurysm sac. Stepwise elevation of length, force recorded as a function of time (with permission of Karger). c. In vivo pressure-diameter pulsatile hysteresis loops recorded in the rabbit thoracic aorta. Each loop corresponds to one cardiac cycle. Taken at different levels of bleeding hypotension. (Nadasy, Csaki, Porkolab and Monos, unpublished).

9. Biomechanics of different vascular segments

9.1 Windkessel artery and distributing artery biomechanics

Elasticity is the very essence of Windkessel artery function (Milnor 1982, Zieman 2005). With each ventricular contraction at rest about 70 ml of blood is pushed into the large arteries, close to the heart. These vessels are containing a fairly large number of concentric elastic sheets intertwined with layers of smooth muscle cells in a fishbone pattern, visibly connecting neighboring elastic sheets. (Clark 1985). At physiological stresses and above them these vessels are more elastic than more peripheral vessels with less elastic tissue (Stemper 2007, Fig. 4b.). With aging and hypertension, rigidity of these vessels increases with a concomitant increase of diameter (Farasat 2008, Giumelly 1999, Safar 2005). In vivo

elasticity is frequently measured in form of *pulse wave velocity* (Huotari 2010, Westerhof 2007), aortic compliance (Long 2004, Mersich 2005), *input impedance* (Mazzaro 2005) or *augmentation index* (Safar 2005). Exercise training can stimulate elastin production and reduce high-stress stiffness (DeAndrade 2010). Elastin production is stimulated by periodic stress, that is, by pulse-pressure. The produced elastin will form parallelly connected sheets, that are fairly stretched even at physiological diastolic pressures and thus take part of the force from smooth muscle and collagen. Diameter to wall thickness ratios can thus be relatively large in elastic vessels. Too large periodicity in stretch, however, will speed up the disintegration of elastic lamellae, a typical feature in aged and chronically hypertensive large arteries (Greenwald 2007). An unsettled question is pulsatile viscosity. We have found a profound hysteresis of the pressure-diameter curves in vivo (Nadasy 2007 and unpublished, Fig. 5c.).

9.2 Resistance artery biomechanics

Resistance arteries have limited amount of elastic tissue, the real arterioles none at all. Their most important function is to offer a relative large but controllable resistance which makes controlled in space and time) flow distribution toward the tissues. They are characterized by relatively thick walls and a large diapason between most relaxed and most contracted diameters (Szekeres 1998, Fig. 3b.) and by massive myogenic response (Fig 4d.). Pulse pressure is dampened usually en route in large arteries, remaining undulations will support only a limited elastica production of medial cells. In hypertension, however pressure undulations can increase in resistance sized arteries with biomechanically and histologically observable elevation in elastin production. In later phases of the disease, however, these elastic lamellae will be disrupted. Similar alterations can happen with aging (Arribas 1999, Briones 2003, Gonzales 2005,2006, Intengan 1998, 2001, Laurant 1997, Nadasy 2010a, Takeuchi 2005). Even more important are the segmental geometry alterations. The great circulatory physiologist Folkow realized first that morphological wall thickening might reduce lumen and stabilize elevated resistance and hypertension. He supposed to happen it with an elevation of wall mass (hypertophic wall remodeling, Folkow 1971, 1990, 1995). Later, Mulvany has proven that morphological restriction of the lumen with increased wall thickness can happen without alteration in wall mass (eutrophic remodeling, Mulvany 1990, 1992). The idea emerged that what essentially happens first is a morphological stabilization of a contracted diameter (Mathiasen 2007, Nadasy 2010a). Now we have a picture that both in hypertension and aging there is a morphological lumen restriction of resistance vessels (Dickhout 2000, Frisbee 1999, James 2006, Jeppesen 2004, Kvist 2003, Matrai 2010, McGuffy 1996 Moreau 1998, Muller-Delp 2002, Mulvany 1996, Nadasy 2010a, 2010b, Najjar 2005, Orlandi 2006, Pose-Reino 2006, Riddle 2003, Rizzoni 2006, Rodriguez-Porce 2006, Stacy 1989, Varbiro 2000). We believe that the fact, that substances inducing immediate blood pressure rise have independent from biomechanical effects trophic action on the resistance artery walls is not contradictory to the biomechanical control theory. With their additional effects on vascular smooth muscle protein expression, in the real situation, they promote existing biomechanical control processes (Nadasy 2010a, Safar 1997, Simon 1994, Toyuz 2005). Even more important than changes in segmental geometry, can be the network alterations. Rarefaction and course deviations in hypertension also increase local resistance (Greene 1989, Harper 1978, Nadasy 2000, 2010b, Prasad 1995).

9.3 Biomechanics of veins

Veins are frequently referred to as being distensible. However, similarly to all vessels, veins also turn rigid when sufficiently stretched (Fig. 4e). Most in vitro and in vivo studies show that the transition between the distensible and rigid sections of the pressure-diameter characteristic curve – similarly to arteries and all other vessels – lies around typical physiological pressures (Berczi 2005, Molnar 2006, Molnar 2010, Monos 1983, 1995, 2003, Raffai 2008, Stooker 2003, Zamboni 1996,1998). That makes it possible to insert venous grafts into the arterial system (Monos 1983).

10. Conclusion

Geometry and viscoelasticity controlled both in the short and long runs. Viscoelastic units, the evidence of mechanically driven continuous vessel wall remodeling. The vascular mechanical failure: A biomechanical explanation for the thick vessel syndrome.

The possibility to produce mechanical work at the expense of chemical energy, the ability to restructure the active and passive force-bearing components, even degrade or synthesize them (vascular remodeling) makes the vascular wall an unusually complicated viscoelastic material.

Short term control of segmental geometry is most effective in resistance arteries. Contraction of the outer circumferential smooth muscle layer – because of the incompressibility of the wall – presses the inner layers into the lumen, inducing substantial decrease in lumen diameter and elevation in wall thickness. The hemodynamic effect will be much increased local vascular resistance. Short term control of elasticity will be an important physiological function of the smooth muscle of large arteries. When contracting, they stress upon the elastic membranes reducing high-stress isobaric elastic modulus of the wall. This improves adjustment of vascular impedance to altered ventricular function. Long term control of vascular lumen will be driven by endothelial shear (to keep it constant, Murray-Rodbard law). Normally, several mechanisms point toward such a balanced situation. Endothelial shear can alter several proteins' expression in the wall, the induced acute vasodilation can morphologically stabilize, agonists released in response to shear might contribute to alteration in the morphological lumen. Even substances with primary tissue effects might have additional direct or indirect vascular effects that help adjust vascular lumen to altered tissue function and blood flow needs (feed-forward control). In a phylogenetically unusual situation, however, such adaptation processes can "derail" and work against formation of an optimal morphological vascular lumen. Vessel wall thickness - on the long term - will be controlled to stabilize tangential stress – if there is no change in tissue composition (Folkow-Rodbard-Mulvany's law). In case of periodic stress, smooth muscle cells will be stimulated to produce elastin (Burton-Roach-Kadar's law), which reduces high-stress modulus. Elastic lamellae produced will bear part of the force, leaving less stress on parallelly connected smooth muscle and collagen, allowing thus lesser wall thicknesses. While the viscoelastic properties of the contributing molecules are poorly described, studies on blood vessels with extreme histological composition suggest that intracellular contractile fibers, elastic tissue and collagen are organized in viscoelastic units. The number of serially and parallely connected such units plastically adapts to lengths and forces applied. There seems to be a stoichiometrically determined connection between series and parallel elasticity and viscosity of such viscoelastic units. Viscosity – together with elasticity – helps even distribution of the forces among the parallelly connected elements of the vascular wall.

Restoration of elongated viscous units will be possible at the expense of ATP energy by smooth muscle contraction, if this viscous elongation happened by breaking up, passive sliding and reformation of "latching" actomyosin cross-bridges (intracellular viscosity). If viscous elongation happens between extracellular fibers, migration, adhesion and contraction of smooth muscle elements, with subsequent connective tissue production fixing the restored length might restore the original situation. Study of aneurysmic tissue, where no contractile elements are present to prevent slow but fatal viscous dilation, make it probable, that such restoring processes are continuously going on in healthy vascular tissues. Based on biomechanical experience, we can suppose that if common mechanisms to distribute the force to smooth muscle and elastic components fail, there is a possibility for the vascular wall to prevent fatal rupture to develop, by increasing the amount of collagen in the wall. By this, however, the adaptation to periodic stresses (large vessels), the ability to control resistance (small arteries) and the ability to reduce stress by contraction (veins) will be lost. With loss of smooth muscle, the "ropes" of collagenous tissue cannot be pulled and fixed together, new and new collagenous masses should be produced to prevent slow passive viscotic creep and fatal rupture. In case of large vessels that will alter the pressure distribution in the radial direction of the wall and will interfere with vasa vasorum blood supply of the vessel wall itself. The "blood vessel wall failure" will have a common course, independently of the original pathology that has induced it. That yields a simple biomechanical explanation for the "thick vessel syndrome" and for its amazing analogies with the aging process.

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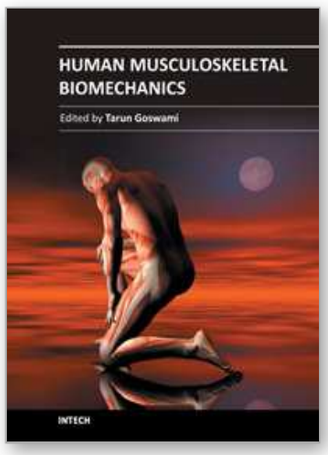

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This book covers many aspects of human musculoskeletal biomechanics. As the title represents, aspects of forces, motion, kinetics, kinematics, deformation, stress, and strain are examined for a range of topics such as human muscles, skeleton, and vascular biomechanics independently or in the presence of devices. Topics range from image processing to interpret range of motion and/or diseases, to subject specific temporomandibular joint, spinal units, braces to control scoliosis, hand functions, spine anthropometric analyses along with finite element analyses. Therefore, this book will be valuable to students at introductory level to researchers at MS and PhD level searching for science of specific muscle/vascular to skeletal biomechanics. This book will be an ideal text to keep for graduate students in biomedical engineering since it is available for free, students may want to make use of this opportunity. Those that are interested to participate in the future edition of this book, on the same topic, as a contributor please feel free to contact the author.

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