Reviews

Remodeling of Resistance Vessels in Essential Hypertension

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The work of Riva-Rocci (1896) and Korotkov (1904) allowed the measurement of branchial systolic and diastolic blood pressure in humans. In 1911, Frank introduced the term "essential hypertonie", which became essential hypertension and this term is now used to indicate hypertension of unknown etiology. For over 100 years physicians have studied the relationship between elevated blood pressure and vascular disease[1]. Nowadays, the study of structural and mechanical alterations of small arteries as well as their possible role in the pathogenesis of essential hypertension still remains a matter of clinical and scientific interest.

The role of small arteries in the pathophysiology of elevated blood pressure is underlined in the definition of essential hypertension: the disease is usually associated with normal cardiac output but increased peripheral resistance[2]. The capillary pressure of essential hypertensive patients is about 17% of systemic pressure, similar to that in normotensive controls[3]. This indicates that the main increase in resistance lies in those pre-capillary vessels that contribute to and control the peripheral resistance. These vessels are known as resistance vessels: the arterioles and the small arteries.

The reason fpr increased peripheral resistance is not known, but physical considerations indicate that either the resistance vessels are narrowed or there is a decrease in the number of parallel-connected vessels, a process known as rarefaction[4-7]. The development of newer techniques for direct visualization, as well as for in vitro examination of the vessels allowed the study of structural and mechanical alterations of arterioles and small arteries in essential hypertensive patients[8]. Although, the pathogenic role of resistance vessels in causing high blood pressure is not yet known, hypertensive damage of arterioles and small arteries contributes to complications of hypertension[9]. Therefore, the study of structural and mechanical alterations of resistance vessels in essential hypertension, the possibility of reversal of these changes with antihypertensive treatment, and their contribution to the prognosis of patients with essential hypertension are nowadays considered of great importance.

This review is focused on the data from vascular remodeling in resistance arteries in patients with essential hypertension.

Mechanisms of vascular remodeling in essential hypertensive patients

Definition

In 1989, Baumbach and Heistad[10] demonstrated that in essential hypertension the changes in the structure of resistance vessels, namely

- the decreased lumen and
- the increased ratio of "media thickness to lumen diameter",

may not be associated with change in the amount of the material of the vessel wall. Baumbach and Heistad defined this ability of resistance vessels to change their structure without changing their volume, as *remodeling*. For many years after this, the term "vascular remodeling" was used alone to describe a change in lumen associated with rearrangement of material. However, this term has also been used to refer to remodeling of the heart after myocardial infarction, to changes in coronary arteries after angioplasty, as well as to describe structural changes of large arteries in hypertension. Remodeling in these different organs and pathological conditions is caused by different processes.

A number of researchers proposed, some years later, that the term "remodeling" should be confined to situations in which there is a structurally determined change in the lumen diameter of a relaxed vessel, measured under a standard intravascular pressure[11]. Remodeling was classified, by the same authors, into six types, depending on the structural changes of resistance vessels in hypertension. It was suggested that remodeling should be termed "inward" or "outward remodeling", depending on whether the process had resulted in a decrease or increase, respectively, in vessel diameter. Furthermore, an increase, no change or a decrease in the amount of the vessel material, sub-classify remodeling into hypertrophic, eutrophic and hypotrophic, respectively. Hypertrophic remodeling is a growth-related process and may involve an increased number of cells (hyperplasia), increased size of cells (cell hypertrophy) and increased deposition of fibrillar or non-fibrillar intercellular matrix or various combinations of these. Hypotrophic remodeling involves a reduction in the amount of vessel material. Eutrophic remodeling is characterized by no change in the amount of the material of the vessel wall, may be a result of rearrangement-restructuring of cellular and non-cellular vessels components, or a combination of growth and apoptosis in the vessel wall. Furthermore, the authors usually use the terms "remodeling index"and "growth index", for the quantification of the remodeling process (see "Addendum")[12].

In accordance with the argument of some authors, remodeling is not necessarily a pathological state, given that in hypertension, the changes in the vasculature may be part of early growth[13].

Mulvany et al have suggested that the term remodeling does not per se imply a pathological or pathogenic change, but rather a difference between vessels of hypertensives and those of normotensives of similar age[14]. Whether a remodeling process also plays a role in the pathogenesis and pathophysiology of essential hypertension remains to be determined.

Resistance vessels structure

The artery wall is composed of three clearly distinct layers: an inner, a medial and an outer[15]. Each layer has a different role concerning the mechanical support of the artery wall, the metabolic function of the vessel and the interaction with the elements of the blood. The three layers are separated by sheets of elastic tissue: the internal and external elastic membrane.

The intima (inner layer) consists of one monolayer of endothelial cells, a subendothelial layer containing connective tissue, the basement membrane, with rare smooth-muscle cells. The basement membrane is mainly composed of collagen type IV, elastin, fibronectin, laminin and proteoglycans, which compose the extracellular matrix.

The media is the muscular support of the artery wall. It is separated from the internal and external elastic membrane. The media layer, in the muscular arteries (e.g. radial artery), consists of dense layers of circumferentially or helically oriented smooth muscles. Each smooth muscle cell (SMCs) is surrounded by an incomplete basement membrane. The number of the smooth muscle layers depends on the artery size.

In the elastic arteries (e.g. carotid), the media is composed similarly of layers of circumferentially or helically oriented smooth muscles. Each layer is surrounded by densely distributed elastic fibers, oriented to the long axis of the SMCs. In the inner section of this dense elastic network an interstice matrice is distributed, consisting of collagen type I, III and IV and of basement membrane, circumferentially oriented, which surrounds the cells and assure their continuity and integrity. The unit "smooth muscle, elastic fibers, interstitial matrix" consist the muscle-elastic layer[16].

The adventitial layer consists of collagens and elastic fibers, fibroblasts, a few SMCs, vessels and a lot of nerve fibres.

Arterioles, arteries with no more than one layer of SMCs and the small arteries (prearteriolar arte-

ries with lumen diameters <300 μm) exert their function as resistance vessels, presenting resistance to blood flow.

Two important parameters for the study of the vessel remodeling are the "wall thickness / lumen diameter" (or "media thickness / lumen diameter") ratio and the cross-sectional wall area[17]. The calculation of the "media thickness / lumen diameter" ratio, according to the Laplace relation, provides information about the ability of the vessels to contract against intravascular pressure**.** The knowledge of wall cross-sectional area indicates the amount of material within the vascular wall and thus provides information about the process of growth or regression.

Mechanisms of resistance vessels remodeling

Vascular remodeling may be considered as a chronic adaptive process, a response of vessels to alterations within their milieu or to changes in hemodynamic variables[18]. The mechanisms of this chronic process are not completely known. The available data indicate that the dynamic interaction between chemical factors and hemodynamic stimuli, may lead to changes in at least four cellular processes:

- Cell growth
- Cell death or apoptosis
- Cell migration and
- Production or degradation of extracellular matrix[19].

The biologic process of vascular remodeling involves the detection of mechanical or chemical signals from the cells, the relay of these signals within the cells, the synthesis, activation or release of substances that influence cellular or non-cellular processes and finally the structural and functional changes of the vessel.

Although all the vascular components may participate in the remodeling process, the endothelium seems to play a prominent role. Even if it is difficult to be determined the relation between dysfunction and vascular remodeling in terms of causality**,** nevertheless, the endothelium is stratically located to serve as a sensor and transducer of signals, but also as an effector cell eliciting biologic responses through the activation or release of substances involved in vascular remodeling[19].

According to a proposed model of the pathophysiologic mechanisms leading to small artery remodeling, elevated blood pressure, either directly or indirectly, via the action of vasoactive peptides and possibly mediated in part by oxidative stress, induces vasoconstriction, apoptosis, SMC growth, inflammation and vascular fibrosis[20].

The role of apoptosis (that is gene-regulated cell death) in vascular remodeling remains unclear. Inward eutrophic remodeling is determined by reduced lumen diameter, increased "media thickness/lumen diameter" ratio and no change in cross-sectional area. In this type of remodeling, a combination of growth and apoptosis (whereas inward growth decreases the lumen diameter, and apoptosis localized to the outer periphery reduces the outer diameter of the vessel) could explain the maintenance of media volume. Nevertheless, it is not yet clear, if apoptosis is a growth related compensatory mechanism or a primary process in vascular remodeling. Experimental studies propose, the reactive oxygen species, NO, the endothelin system and angiotensin type 2 (AT2) receptors as possible apoptosis modulators[20, 21].

The role of inflammation in the small arteries remodeling process has recently been studied. It is likely that inflammation and the increased oxidative stress may be involved in small and large vessels remodeling in hypertension[20]. It has been proposed that the actions of angiotensin II are mediated to a large measure by stimulation of production of superoxide anion and activation of redox-sensitive genes[22]. Some of these include genes associated with upregulation of factors, such as chemokines, participating in inflammatory response to angiotensin stimulation.

Cell growth may be manifested as hypertrophy or hyperplasia of myocytes. The available evidence suggests that in small arteries remodeling in essential hypertension, the number and size of SMCs is normal, in contrast with the type of remodeling observed in large arteries, in some forms of experimental and secondary hypertension [23].

Vascular fibrosis involves changes in extracellular matrix (EXC) components, which are the structural proteins (collagen, elastin*)* and adhesive proteins, as laminin and fibronectin. Collagen has been reported to increase in mesenteric small arteries of spontaneously hypertensive rats (SHR) but also in resistance arteries in essential hypertensive humans[24]. Augmented deposition of extracellular proteins in the vessel wall seems to be, to a large extent, a humoral-determined event. Angiotensin II, endothelin-1 and mineralocorticoids appear to play

a central role in this process. Angiotensin II stimulates human vascular SMCs production of collagen I, via AT1 and possibly AT2 receptors[20]. Moreover, several reports have indicated that angiotensin converting enzyme (ACE) blockade has specific effects on EXC matrix metabolism, modifying fibronectin expression and collagen accumulation. These changes were shown to be more closely related to ACE inhibition in arterial tissue than to arterial pressure reduction[25].

Furthermore, matrix metalloproteinases (MMPs) play a prominent role in alterations of EXC components in hypertensive patients[26]. MMPs are Ca^{2+} and Zn^{2+} -dependent proteolytic enzymes that degrade EXC matrix proteins. Several different MMPs are present in the vasculature. Changes in MMPs activity or in biochemical balance with their natural inhibitors, may contribute to resistance artery remodeling, by modulating the composition of EXC matrix and also the structure of the vessel wall.

In conclusion, the above mechanisms may contribute to the chronic process of remodeling in essential hypertension. Further investigation of the mechanisms involved in this process as well as possible development of therapies that contribute to reversal of the vascular remodeling are the object of current studies.

Structural, functional and mechanical alterations of resistance vessels in essential hypertension

Structural alterations

The available information regarding resistance arteries structure in essential hypertension is influenced by the study method. Nevertheless, most of the data agree on the type of resistance arteries structural alterations in essential hypertensive patients[27].

The first evidence for altered resistance vessel structure was derived from autopsy studies, in the 19th century[28]. Those studies indicated that the small arteries of hypertensive patients had an abnormally high "wall / lumen" ratio. In vivo hemodynamic experiments, by Folkow, about one century later, supported that finding[29].

Further evidence came later, with the development of the technique of gluteal skin biopsy taken under local anesthesia, from which it is possible to isolate small arteries for mounting on wire-myographs.

The majority of the available data indicates that, in essential hypertension, the resistance arteries show a reduced lumen diameter, increased ratio of "media thickness / lumen diameter" and unchanged cross-sectional area of the media[30-33]. The cellular basis of these morphological alterations has been investigated. Thus, the relative information suggests that the myocyte size within the media is normal[34]. Thus, most reported data indicate that, in essential hypertension, the resistance vessels have experienced inward eutrophic remodeling. The "collagen / elastin" ratio, which determines to a large extent the elastic properties of the artery, has been reported to be normal or increased[16].

However, in a recent study, where resistance arteries were studied by the method of pressurized system and electron microscopy, an increased "media-to-lumen" ratio, normal medial cross-sectional area and an increased growth index have been shown, suggesting a trend toward to what has been designated as hypertrophic remodeling[24].

The heterogeneity of individuals with essential hypertension, but also the difficulties in studying the structure of small arteries with the available methods, may account for some of the confliction in the published data regarding the resistance vessels remodeling.

Functional properties of resistance vessels

Evidence concerning the threshold sensitivity of the vasculature of essential hypertensive patients is sparse. The vasculature in the forearm and the hand shows no abnormality concerning noradrenaline sensitivity[29]. However, other studies have shown that the ratio between the sensitivity of the forearm vasculature of essential hypertensives to calcium antagonists and to nitroprusside was increased[35]. Also, Ljungman et al reported, a slight increase in the sensitivity to venous infusion of angiotensin II in the renal vasculature[36]. On the contrary, the response to endothelin is reduced in small arteries of essential hypertensives, possibly due to enhanced expression of the endothelin-1 gene[37].

Furthermore, several groups of investigators have demonstrated that patients with hypertension have impaired endothelium-dependent vasodilation to acetylcholine in both the peripheral and the coronary circulations[38]. The response to endothelium-independent agent sodium nitroprusside is not reduced, demonstrating that the ability of vascular

smooth muscle to respond to nitric oxide is preserved in these patients.

Effective antihypertensive treatment may normalize or at least improve endothelial vasodilator function. ACE inhibition therapy improves endothelial dysfunction regardless of its antihypertensive effect, as suggested by the TREND study[39]. On the other hand, studies have shown that clinically effective antihypertensive therapy does not modify the vascular response to acetylcholine, indicating that endothelial dysfunction is either a primary phenomenon or becomes irreversible once the hypertensive process has become established[40].

Mechanical properties of resistance vessels

Stiffness, distensibility and compliance are terms that have been used to quantify the elastic properties of the arteries (Table 1)[41].

Compliance, that is the ability of the vessel to buffer changes in pressure, depends on the geometry and stiffness of the wall components of the vessel. Decreases in lumen size, mainly resulting from remodeling in essential hypertension, may reduce compliance. However, vascular compliance may be normalized by decreases in stiffness of wall components[24]. Elastic modulus is geometry-independent and depends on the stiffness of the vessel wall components. Thus, elastic modulus is determined by the combined elastic modulus of the structural components of the vascular wall, that is connective tissue, elastin and collagen fibers, SMCs and endothelial cells.

Table 1. Indices of arterial stiffness.

Elastic modulus	$\Delta P \cdot D/\Delta D$ (mmHg)	The pressure required for (theoretical) 100% stretch from resting diameter at fixed vessel length
Arterial distensibility	$\Delta D/(\Delta P \cdot D)$ (mmHg)	Relative diameter (or area) change for a pressure increment; the inverse of elastic modulus
Arterial compliance	$\Delta D/\Delta P$ (cm/mmHg)	Absolute diameter (or area) change for a given pressure step at fixed vessel length
Young's modulus	$\Delta P \cdot D/(\Delta D \cdot h)$ (mmHg/cm)	Elastic modulus per unit are
Pulse wave velocity	Distance/Δt (cm/sec)	Speed of travel of the pulse along an arterial segment
Stiffness index	$\beta = \frac{\ln(Ps/Pd)}{(Ds-Dd)/Dd}$	Ratio of logarithm (systolic/diastolic pressures) to (relative change in diameter)

ΔP: pulse pressure; D: arterial diameter; ΔD: arterial diameter change; Distance: the distance between the two measuring sites along the arterial tree; Δt: time delay; Ps: systolic pressure; Pd: diastolic pressure; Ds: end-systolic diameter; Dd: end-diastolic diameter; h: arterial wall thickness.

The structure, as well as the mechanical properties of small arteries are altered in essential hypertension. However, changes in the vessel wall structure may not always explain the observed changes in wall mechanics[42]. In very small arteries from the brain, the pioneering studies of Baumbach et al showed that wall mechanics might not be altered as expected[43]. It has been shown that vascular compliance is not necessarily reduced in hypertension, despite increased media thickness of the vessel wall and, in some vascular beds, increased collagen deposition.

Studies in small arteries (<150 μm in lumen diameter) from the brain of SHR, demonstrated that the composition of vessels was altered, with increased elastin content, which could explain the reduced wall stiffness and the maintenance or even increase in compliance and distensibility of the arteries[43]. Findings in large arteries from animal models and humans, suggest that a reduced stiffness of wall components is indeed a common characteristic in hypertension[44]. The mechanism may not be the same for all vascular beds, in humans and animals, in which the ratio "collagen / elastin" may be increased or unchanged[16]. In their study, Intengan and colleagues have shown increased "collagen to elastin" ratio in resistance arteries of essential hypertensive patients, but decreased stiffness of wall components and maintenance of mechanical properties[24].

The mechanisms involved in the maintenance or increased compliance of small arteries remain unclear. Since differences in the volume density of the media-components, more or less distensible, do not appear to play a prominent role, the direction of the alteration in wall mechanics could be related in part to the organization of these components in the arterial wall. Changes in the arrangement, alignment and adhesion of cellular and fibrillar elements might be involved in changes in mechanical properties of resistance arteries. Intengan and Schiffrin have proposed that remodeling of the small arteries occurring in both humans and experimental models of

hypertension implies a remodeling of the EXC matrix and of extracellular-vascular SMCs attachment sites and a restructuring of vascular SMCs that may be in part triggered by the adhesion molecules (integrins) that can transduce signals from the extracellular to the cytoskeletal fibrillar components[20,45]. Changes in EXC matrix components and corresponding adhesion receptors, interactions between SMCs and matrix proteins may result in rearrangement and restruction of EXC matrix and SMCs in the vascular wall.

Thus, the EXC matrix may not be considered only from the point of view of its quantitive elastic properties. The arrangement as well as the interactions of wall components also has to be taken into consideration, since alterations in the volume of the EXC matrix proteins (collagen, elastin) may not always explain the consequences of structural changes on mechanical properties of the vessels[16]. Fibronectin, laminin and the integrins may be involved in the process of resistance artery remodeling[46,47].

The altered mechanics of the resistance arteries may affect hemodynamic parameters, such as the pulse wave, wave reflection, blood flow velocity and accordingly shear stress, contributing to vascular damage. Vascular damage and cardiovascular risk may be modified by changes in wall mechanics. Decreases in the stiffness of wall components could protect the vessel wall[48].

The mechanisms of altered elastic properties of resistance vessels in different vascular beds, as well as the extent to which changes in mechanics are protective and whether they may contribute to the estimation of cardiovascular risk, remain to be determined.

Measurement of resistance vessels remodeling

The structure of small vessels with the currently available techniques can be studied by obtaining a biopsy of skin or subcutaneous tissue, for dissecting and studying the artery in vitro. The method, used for the first time by Aalkjaer et al, has the advantage of studying samples from selected hypertensive patients, before and after chronic antihypertensive therapy, allowing for the assessment of characteristics of these vessels before and after treatment[30].

Biopsies, to obtain small arteries have been performed on tissue from the gluteal region or the distal anterior forearm. Once the arteries have been isolated, there are essentially two techniques for the investigation of human small arteries: the wire myograph method and the pressurized artery preparation[14].

These techniques can be used for the study of: (a) morphometric parameters of small arteries, such as the media width, the cross-sectional area, the lumen diameter, (b) remodeling and growth index and (c) mechanical properties of the vessel wall, such as elastic modulus, that describes the intrinsic elastic properties of the wall material. Both techniques can be followed by histological examination of fixed vessels.

To study small arteries on the wire myograph two wires are threaded through a small vessel, which is then stretched to an arbitrary degree that has been shown to result in the optimal magnitude of active tension development in response to agonist stimulation. In the pressurized preparation, the vessels are slipped onto two glass microcannulae, one of which is fixed and the other can be positioned as appropriate. Vessels are usually exposed to pressures of 30-60 mmHg, and changes in lumen diameter are measured during video imaging.

Both methods show disadvantages in the measurement of morphometric parameters of small arteries[14]. Nevertheless, the results of comparative studies of vessels from hypertensive and normotensive individuals can be reproduced and the wire- and pressure-myograph techniques provide qualitatively consistent results[27].

Moreover, two important parameters have to be considered in the evaluation of the results of in vitro studies of small arteries remodeling: the site of the vascular tree from which the study vessel has been dissected and the conditions of intravascular pressure under which morphometric characteristics and mechanical properties have been examined[49,50].

In the future, the difficulties in studying the structure of small arteries will be overcome, with the development of new techniques that will permit their non-invasive investigation. Doppler study with higher frequency transducers will allow the measurement of wall thickness even in small arteries.

Antihypertensive treatment and reversal of resistance vessels remodeling

Although the pathogenic role of small arteries and arterioles in causing high blood pressure is not clear, the structural and mechanical alterations of resistance vessels seem to contribute to complications of hypertension, such as strokes[12], nephroangiosclerosis[51] and possibly to myocardial ischaemia[9].

Thus, the study of possible regression/reversal of structural and mechanical changes of resistance vessels with antihypertensive treatment and whether normalization of the structure and function will improve clinical outcomes of hypertensive patients, is of great interest.

In the past few years, in vitro studies of resistance vessels have shown that reversal of hypertension with most classes of antihypertensive drugs can lead to normalization of resistance vessels structure. The general finding has been that normalization of blood pressure in essential hypertensive patients results in normalization of structure and function, this being the case for treatment with angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists. Mulvany et al suggested that normalization of the abnormalities in the structure of resistance vessels, should be obtained not so much by inhibition of growth, but by facilitation of remodeling, i.e. a rearrangement of the wall material around a larger lumen[52].

Schiffrin, in a relevant review, suggested that in hypertensive patients in whom blood pressure is equally controlled, treatment with these two classes of antihypertensive drugs, might lead to reversal of structural and functional changes that occur in small arteries[53]. Moreover, the reversal of these changes concern all vascular beds and may also occur in coronary microcirculation[53,54].

The structural parameter that these studies have focused on is the "media thickness-lumen diameter" ratio of small arteries. According to the author, this is a highly stable and reproducible parameter and furthermore is of major hemodynamic significance, since it was recently shown to correlate closely with minimal vascular resistance at maximal vasodilation in small arteries.

Moreover, calcium antagonists and ACE inhibitors appear to be equally effective in normalizing endothelial dysfunction[53]. A notable exception has been b-blocker treatment without intrinsic sympathomimetic activity, in which atenolol did not cause normalization of resistance vessels structure and function, even when administered for up to 2 years[53,55]. The reason for the differential effect of different classes of antihypertensive drugs is not clearly understood. It might be related to the different pharmacological action of these drugs. Nevertheless, one in vitro myograph study showed no effect of isradipine on small arteries structure[56].

Recent data have demonstrated that antihypertensive treatment with the AT1 receptor antagonist losartan improve structural abnormalities and normalize the endothelial function of small arteries from hypertensive patients[57].

The action of diuretics on vascular structure is not clear. There is conflicting data in the literature regarding the effect of diuretic treatment on normalization of resistance vessels structure[58,59].

Is normalization of resistance vessels structure necessary for successful antihypertensive therapy? The available data suggest that the resistance vessels should be considered a neurohumoral target and that remodeling have an amplifier effect on the complications of hypertension[52].

Therefore, it could be proposed that normalization of the structure is not necessary for successful antihypertensive therapy. Nevertheless, reduction in blood pressure without normalization of resistance vessels structure would reduce the vascular reserve. Consequently, the decreased coronary vascular reserve would be exacerbated rather than relieved[9,52].

It seems that altered resistance vessels structure is a major characteristic of hypertensive disease and may be one of the fundamental causes of the observed reduced vascular reserve. Therefore, normalization of the structural, functional and mechanical properties of resistance vessels has to been seen as an important goal of antihypertensive therapy.

Further investigation is now required to determine whether reversal of resistance vessel remodeling with antihypertensive treatment will also improve clinical outcomes of essential hypertension, reducing morbidity (cardiac events, strokes, progression of hypertensive nephropathy) and mortality.

Addendum

$$\text{Remodeling index} = 100 \times \frac{[(Di)n-(Di)remod]}{[(Di)n-(Di)h]}$$

$$\text{Growth index} = \frac{CSAh-CSAn}{CSAn}$$

Where:
(Di)n and (Di)h are the internal diameters of normotensive and hypertensive vessels, respectively,
(Di)remod is the remodeled internal diameter,
CSAn, is the cross-sectional area of normotensive vessel and
CSAh, is the cross-sectional area of hypertensive vessel.

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