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Review

Hypertension and microvascular remodelling

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In the present review, microvascular remodelling refers to alterations in the structure of resistance vessels contributing to elevated systemic vascular resistance in hypertension. We start with some historical aspects, underscoring the importance of Folkow's contribution made half a century ago. We then move to some basic concepts on the biomechanics of blood vessels, and explicit the definitions proposed by Mulvany for specific forms of remodelling, especially inward eutrophic and inward hypertrophic. The available evidence for the existence of remodelled resistance vessels in hypertension comes next, with relatively more weight given to human, in comparison with animal data. Mechanisms are discussed. The impact of antihypertensive drug treatment on remodelling is described, again with emphasis on human data. Some details are given on the three studies to date which point to remodelling of subcutaneous resistance arteries as an independent predictor of cardiovascular risk in hypertensive patients. We terminate by considering the potential role of remodelling in the pathogenesis of end-organ damage and in the perpetuation of hypertension.

Hypertension elicits two different kinds of diffuse structural changes in the systemic microcirculation. One, termed *rarefaction*, consists in an abnormally low spatial density of arterioles, capillaries, and possibly venules. The other concerns structural modifications of resistance small arteries and arterioles, which lead to a reduction in lumen diameter and are grouped under the generic name of *remodelling*. We have recently reviewed rarefaction in detail.[1] The focus of the present paper is on remodelling which probably accounts for the major part of long-term elevation of systemic vascular resistance (SVR) in hypertensive patients.

1. Historical note

The first intellectual association of hypertensive disease with diffuse abnormalities of the microcirculation may be traced back to Richard Bright, a father of nephrology, who in the third decade of the 19th century brilliantly described the natural course of what became to be known as Bright's disease, in fact a heterogeneous class of chronic nephropathies. Bright noted the presence of a hard pulse[2] and the frequent autopsy finding of left ventricular hypertrophy unexplained by gross cardiac or aortic defect.[3] In the excerpt shown in *Figure 1*, one may follow the line of thought which led Bright to hypothesize a diffuse microcirculatory derangement. In 1869, George Johnson provided the first histological evidence of wall thickening in small arteries of various organs obtained at the autopsy of patients who suffered from Bright's disease (*Figure 2*).[4] Johnson was well aware that blood pressure in Bright's disease was abnormally high. A decade later, the concept that heightened blood pressure may precede and be a cause rather than a consequence of altered microvascular architecture was introduced by Ewald,[5,6] who was also the first to propose the ratio of wall thickness to lumen diameter for the assessment of abnormal microvessel structure.[7] Of note, it is only later, i.e. in the first two decades of the 20th century, that essential hypertension became established as a nosographic entity.[6] The first quantitative study of arteriolar structure in hypertensive disease, using modern histological methods as well as a relatively crude form of morphometry, was published in 1929 (*Figure 3*).[8] In the ensuing decades, the discovery of the Goldblatt's models and the renin–angiotensin system were important factors explaining that the focus of hypertension research shifted towards functional and away from structural aspects of resistance vessel abnormalities.[6,9] The pioneering work of Björn Folkow started the pendulum moving in a different direction, demonstrating that hypertension was associated with abnormally high resistance to blood flow, even in maximally dilated vascular beds, a strong evidence for the haemodynamic importance of altered microvascular structure (as opposed to altered vascular tone) in the

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TABULAR VIEW

OF THE

MORBID APPEARANCES IN 100 CASES

CONNECTED WITH

ALBUMINOUS URINE.

WITH OBSERVATIONS.

BY DR. BRIGHT.

The obvious structural changes in the heart have consisted chiefly of hypertrophy with or without valvular disease: and what is most striking, out of fifty-two cases of hypertrophy, no valvular disease whatsoever could be detected in thirty-four: but in eleven of these thirty-four, more or less disease existed in the coats of the aorta; still, however, leaving twenty-two without any probable organic cause for the marked hypertrophy generally affecting the left ventricle. This naturally leads us to look for some less local cause, for the unusual efforts to which the heart has been impelled: and the two most ready solutions appear to be, either that the altered quality of the blood affords irregular and unwonted stimulus to the organ immediately; or, that it so affects the minute and capillary circulation, as to render greater action necessary to force the blood through the distant sub-divisions of the vascular system.

Figure 1 Title and excerpt from Richard Bright's original report The black bar in the margin draws attention to the mention made of the microcirculation. The excerpt straddles pages 396 and 397 in the original publication.[3] Reproduced with permission by ISS Enquiry.

hypertensive circulation.[10] It took however a good additional 20 years before systematic interest progressively developed in other groups of investigators for the vascular structural factor in hypertension.[11–14]

2. Definitions and basic concepts

2.1 Resistance vessels

Resistance vessels are those which concentrate the major part of the pressure drop that must occur between large conduit arteries and capillaries. It has been underscored that their exact anatomical location is hard to define precisely,[15] but they are commonly believed to encompass small arteries and arterioles, with diameters ranging from 300 to 15 μm.[16] Resistance vessels are characterized by the presence of *myogenic tone*, i.e. their intrinsic ability to contract in response to a sudden increase of transmural pressure.[1] Important to note, myogenic tone becomes more and more vigorous as vessel size decreases.[17]

2.2 Structural design and adaptability of blood vessels

A fundamental tool to understand the varying structure of different blood vessels in different conditions is the Laplace law, which for any tubular element with cylindrical geometry relates intramural stress (σ), wall thickness (W),

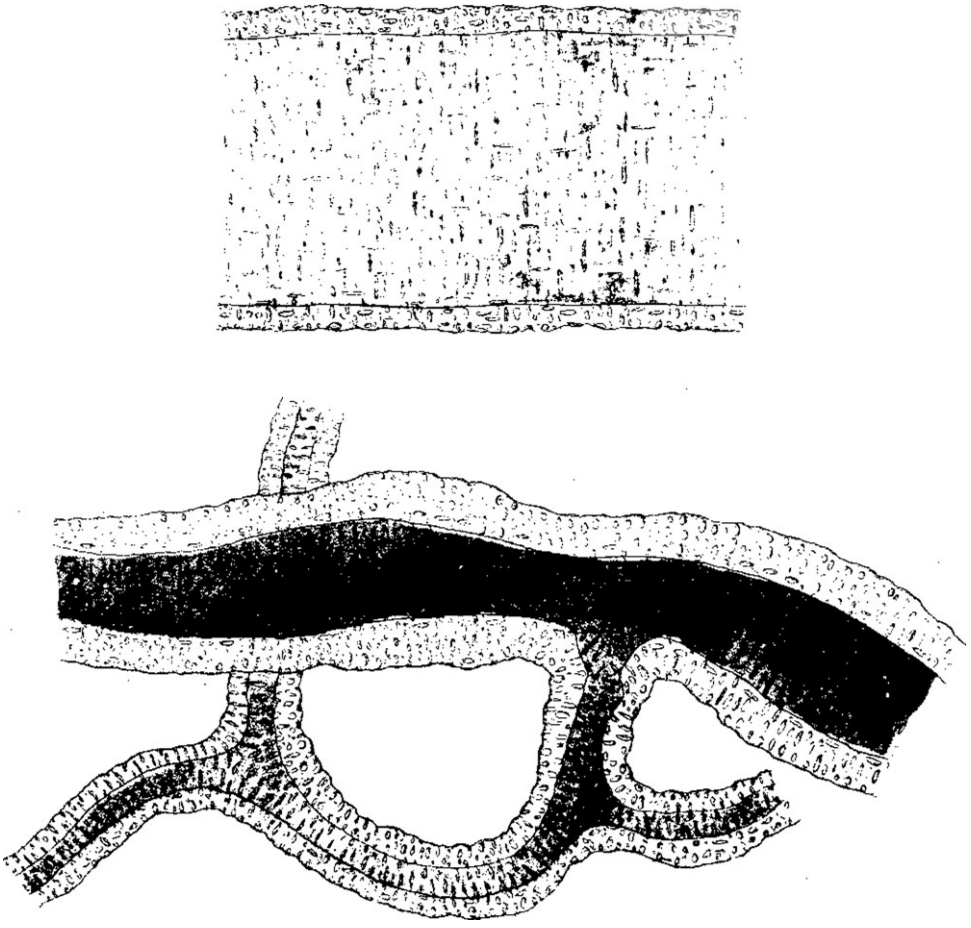

Figure 2 First description of wall thickening of small arteries in hypertension. These drawings are taken from the 1868 paper by George Johnson.[4] They represent microscopic views of small skin arteries, one normal (upper drawing) and one from a patient who at autopsy presented with an abnormal kidney and left ventricular hypertrophy (lower drawing). Reproduced with permission by RSM Publishing.

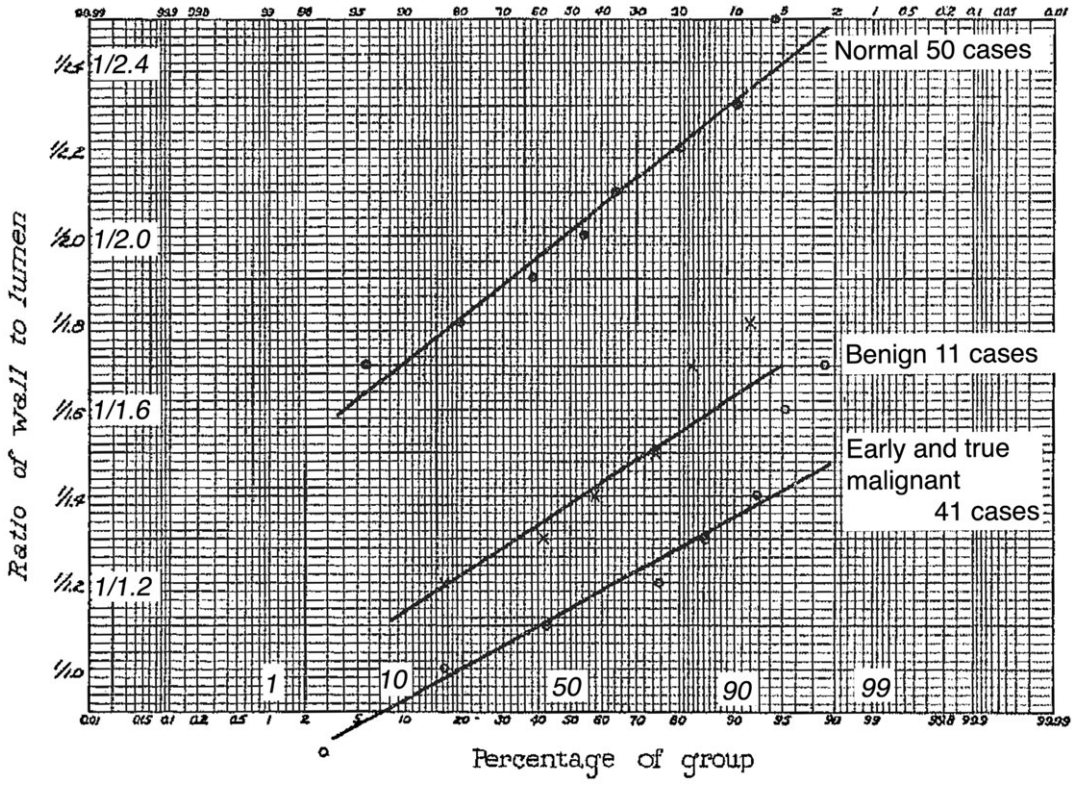

Figure 3 First quantitative evidence of abnormal resistance vessel structure in hypertension.[8] Data from biopsies of the pectoral muscle carried out in 50 normtensive subjects (upper curve), 11 patients with "benign" hypertension (middle curve), and 41 patients with malignant hypertension (lower curve). The mean ratio of wall thickness to lumen diameter was measured in arterioles and small arteries (25–100 μm). To help legibility, the original figure has been overlaid with repeats of some labels. Reproduced with permission from the American Medical Association © 1929. All Rights reserved.

lumen radius (*r*), and transmural pressure (*P*, the difference between luminal and extraluminal pressures) according to the equation:

$$\sigma = \frac{Pr}{W}$$

which may be rewritten in terms of the *W* to lumen diameter (*D*) ratio as

$$\sigma = 0.5\frac{P}{(W/D)}$$

Laplace law dictates vascular structure so as to maintain σ within a relatively tight domain across vessel type, species, and conditions. Within an individual, there is high plasticity of vascular structure, which continuously adapts to accommodate changing conditions of mechanical load, as in fact do other organs such as skeletal muscle and bone. This is well exemplified by the thickness difference between systemic and pulmonary conduit arteries, which is non-existent in the foetus, and develops only after closure of the ductus arteriosus.[18] Evidence of plasticity beyond the developmental stage is given by the wall thickening of venous grafts exposed to systemic pressure.[19]

2.3 The Folkow hypothesis

In his pioneering work already mentioned, Folkow used plethysmography to measure forearm blood flow *under conditions of maximal vasodilation*, and from that he derived the minimal resistance (Rmin) of this vascular bed.[9,10] Forearm Rmin was found abnormally high in hypertensive subjects, an observation which, along with other data gathered in these experiments, was taken as evidence that a structural factor contributed to elevate systemic vascular resistance in these patients. In a bold intellectual move, Folkow proposed that structural alterations could lead to increased resistance even at normal levels of vascular tone. In simplified form, reasoning was as follows. First, even minor reductions in lumen diameter (*D*) may have major effects on vessel resistance, because the latter is inversely proportional on the fourth power of the radius (Poiseuille law). Second, hypertensive structural alterations of resistance arteries consist in wall thickening and increased *W*/*D* ratio, with wall elements encroaching on the lumen, hence structurally reducing *D*, and increasing Rmin. Third, in conditions of increased *W*/*D* the same level of vascular tone, causing the same shortening of SMCs, leads for simple geometrical reasons to a greater reduction of *D*. In other words, the structurally modified resistance arteries in hypertension function as *amplifiers* of vascular tone, which thus needs not be augmented for vascular resistance and blood pressure to be higher than in the normotensive state.

Folkow's view permeates all contemporary thinking on the pathogenesis of elevated blood pressure in chronic hypertension. It is now widely accepted that, important as its is, vascular tone is only a short-term modulator, while structural adaptation of resistance vessels is an obligatory

requirement for elevated blood pressure to be maintained for any prolonged period.[20–23]

2.4 Further concepts

Folkow's hypothesis has both the advantages and disadvantages of simplicity. Notably, it focuses on σ as the single determinant of vascular structural reshaping, while the shear stress (τ) generated on endothelial lining by flowing blood is now of recognized importance. A durable increase in σ is counteracted by an augmented *W*/*D* ratio,[9] but a durable increase in τ results in structural augmentation of *D* (thus tending to reduce blood velocity).[24] Adding to complexity, σ and τ are highly interdependent. For example, the higher *D* resulting from an increase in τ tends to raise σ by virtue of the Laplace law. Pries *et al.*[25] obtained extensive geometrical and mechanical data in the relaxed mesenteric vasculature of anesthetized rats. This enabled them to construct a sophisticated mathematical model of this vascular bed, which notably included the following: (i) several hundreds of vessels, arteriolar, capillary, and venular, (ii) the non-Newtonian nature of blood flow in small vessels ($D <$ 300 μm);[26] (iii) quantitative rules which applied uniformly across all vessels in the network, everywhere relating σ, τ, geometry, blood flow, transmural pressure, and additional factors such as metabolic demand.[27] This model faithfully reproduced the structural changes observed experimentally in the mesenteric circulation of hypertensive rats.

2.5 Vascular remodelling

2.5.1 Nomenclature

In the historical work cited above, the increased *W* of hypertensive resistance vessels was uniformly ascribed to a higher volume of wall material per unit length of vessel [increased wall cross-sectional area (CSA)], or 'hypertrophy'. It was assumed that smooth muscle cells in resistance vessels behaved as did left ventricular myocytes in the face of the increased pressure load, and that growth took place mainly on the luminal side, leading to a structural reduction of internal diameter (*D*). In 1966, Short[28] carried out a careful quantitative geometrical analysis of intestinal small arteries and arterioles in patients with essential hypertension. He observed that, although *W* of these vessels was higher, and *D* smaller than in normotensive controls, media CSA was the same in the two groups of subjects. This finding was not compatible with a structural alteration of hypertensive vessels due to growth alone. The term *remodelling* was first applied to resistance vessels by Baumbach and Heistad,[29] based on observations made in pial arterioles from stroke-prone spontaneously hypertensive rats (SPSHRs), to indicate a structural rearrangement of existing wall material around a smaller lumen.

Noting that the narrow definition adopted by Baumbach and Heistad conflicted with other usages of the same term (i.e. myocardial remodelling), Mulvany[30] proposed that vascular remodelling should encompass any change in *D* noted in a fully relaxed vessel, not explained by a change in transmural pressure or compliance, and therefore due to structural factors. In addition, a two-way classification scheme was put forward (*Figure 4*). Remodelling could be *inward* or *outward*, depending on whether *D* decreased or increased, and *hypertrophic*, *eutrophic*, or *hypotrophic* if respectively contributed to by net growth (increased CSA),

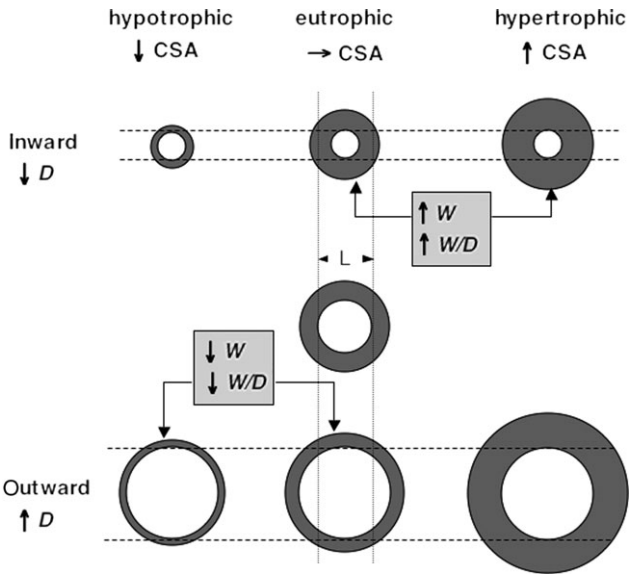

Figure 4 Subtypes of vascular remodelling. Each pair of concentric circles represents a vessel in cross-sectional view. Depicted in the centre of the figure is the reference state, with respect to which structural changes occur. CSA wall (or media) cross-sectional area. *D*, lumen diameter. *W*, Wall thickness. Modified from ref.[30], with author's permission.

no net change in amount of tissue (constant CSA), or net loss of tissue (decreased CSA). With that terminology, the structural abnormalities noted by Short in intestinal arterioles[28] are of course described as inward eutrophic remodelling. For elementary geometrical reasons, inward eutrophic and hypertrophic remodelling are always associated with increased W and W/D ratio, the opposite being true of outward eutrophic and hypotrophic remodelling[30] (*Figure 4*).

The terminology just described has spurred some controversy.[31,32] Importantly, eutrophic remodelling should not be construed as necessarily and exclusively implying rearrangement of existing components.[33] Mulvany's[32] terminology may indeed pose problems if automatically equated with distinct pathophysiological processes, but remains useful as long as no *implicit* assumptions are being made on underlying mechanisms.

2.5.2 Methodology

To be operational, the classification shown in *Figure 4* necessitates appropriate methods for the measurement of resistance vessels dimensions. This problem is much harder than would seem at first sight.[31]

To meet the definition of remodelling given above, the respective sizes of hypertensive and normotensive small arteries and arterioles must be compared with the influence of the following factors either removed or controlled for: (i) vascular tone, (ii) transmural pressure, and (iii) vessel compliance. Obviously, none of these requirements would be met by geometrical measurements made on standard histological sections prepared without perfusion of the tissue sample (e.g. shrinking artefacts).

One widely used approach, possible with small arteries (100 and 300 μm), is to carry out geometrical measurements on dissected segments put in standardized conditions *in vitro*. The segments are mounted in an organ chamber

(myograph), fully relaxed by applying a vasodilator in maximal concentration, and then distended in a standardized fashion. There are two variants of this approach, one using the wire myograph (the most ancient one),[34] and the other the pressure myograph. In addition to standardized geometry, both methods allow detailed measurements of passive mechanical properties, thus making it possible to distinguish alterations in geometry due to changes in wall elasticity from those due to other causes (i.e. remodelling *stricto sensu*). The disadvantages of myography are 2-fold. The first one has been called the sampling problem.[33] Whether the arterial segments assessed with this approach are representative of resistance vessels in the studied organ (not to speak of the whole organism) is open to question. More subtly, for meaningful comparison of hypertensive and normotensive state, it is necessary that the vascular tree be sampled at identical branching level in both conditions, but verification of this requirement is not easy. The second disadvantage of myography resides in the partly arbitrary choice of transmural pressure under which geometry is measured. In particular, one may question the appropriateness of setting this variable at the same level for hypertensive and normotensive vessels, as most studies reviewed below have done.

3. Morphologic evidence for remodelling of small vessels in untreated hypertension

3.1 Animal data

A considerable amount of studies have investigated structural alterations of resistance arteries and arterioles in a large variety of hypertensive models, mostly in the rat, with relatively little work done in other species. The majority of studies have used a popular model of genetically determined hypertension, the SHR. A fundamental problem with this model is the lack of rigorous normotensive controls, since the Wistar-Kyoto rat (WKY) used to that effect differs from the SHR by many genetic markers, only a minority of which are linked to hypertension.[35] To mitigate this concern, alterations of microcirculatory structure broadly similar to those demonstrated in SHRs have been found in several other models for which fully adequate controls exist, such as transgenic rats expressing the mouse Ren-2 renin gene (mRen-2),[36–39] or rats made hypertensive by surgical (Goldblatt)[40–42] or pharmacological means.[43–45]

In a variety of hypertensive animal models (both genetic and secondary), media hypertrophy seems progressively less important as vessel size decreases, whereas eutrophic remodelling is most readily observed in the more distal part of arterial microcirculation.[36,42,46–48] For example, Miller *et al.*[46] have examined perfusion-fixed submucosal intestinal 1A (largest) to 4A (smallest) arterioles from SHRs. While the *W*/*D* ratio was abnormally high in hypertensive vessels of all sizes, only at the 1A level was media CSA increased in comparison with WKY controls. In mRen-2 transgenic rats,[36] impressive media hypertrophy was found in the large main mesenteric arteries,[37] while inward eutrophic remodelling predominated further downstream in this vascular bed.[36] Similar observations of large vs. small mesenteric[47] and kidney[48] arteries are available in SHRs. Below, we shall provide a simple mechanical explanation to this pattern of proximal hypertrophic, progressively blending into distal eutrophic (at times hypotrophic) remodelling.

The definition of remodelling includes the requirement that changes in *D* and *W*/*D* at comparable distending pressure should not be due to altered wall elasticity. In the paper that originated the concept of eutrophic remodelling, as already mentioned, pial arterioles of SPSHRs had reduced *D* increased *W*/*L* and increased distensibility in comparison with those of normotensive controls, thus ruling out stiffening of vessel wall as a cause of the observed morphological alterations.[29] Similar conclusions were reached in several,[49,50] but not all studies.[38,51]

Whether an abnormally high media CSA reflects cellular hypertrophy or hyperplasia has received variable answers. In general, there has been evidence of smooth muscle cells hyperplasia (with or without hypertrophy) in SHRs[43,47] and SPSHRs,[52] i.e. genetic models, whereas SMC hypertrophy without hyperplasia was found in models of secondary hypertension.[41,43] This difference between models may be related to the particular ability of SHR's fibroblasts and SMCs to multiply rapidly under the influence of growth factors.[33] However, this trait is of doubtful relevance to the pathogeny of hypertension, because it does not cosegregate with blood pressure in SHR/WKY F2 hybrids.[33]

3.2 Clinical data

The most feasible possibility for quantitative structural studies of resistance vessels in humans relies on the examination of small muscular (presumably resistance) arteries from biopsies of subcutaneous gluteal fat carried out under local anaesthesia. Small arteries can also be obtained from omental fat excised at the time of abdominal surgery.[14,53,54] The dissected vessels are mounted in a wire or pressure myograph and characterized with the aforementioned methodology. Due to the invasive character of these procedures, most relevant studies are of modest size, typically involving between 10 and 20 subjects per group (with a few notable exceptions[55–57]). Furthermore untreated hypertensives are often patients in whom medication was withdrawn for a few weeks, rather than being newly diagnosed. With these caveat in mind, one may read in *Figure 5* summary of the available information on the comparative structure of small subcutaneous[12,14,51,53,55,56,58–71] or omental[14,53] arteries from untreated hypertensive and normotensive human subjects, as obtained with the wire[12,14,53,55,56,58–68] or pressure[51,69–71] myograph methodology. In non-diabetic essential hypertensives, all data converge on a pattern of reduced *D*, increased *M*/*D* ratio (*M* denoting media width, measured in preference to the total wall thickness *W* in all these studies), and constant media CSA. Not all of these studies have checked vascular mechanics, but when this was done, the wall stiffness of hypertensive vessels was either unchanged[54,71] or slightly decreased.[51] These aggregated data indicate that small subcutaneous arteries of non-diabetic hypertensives undergo inward eutrophic remodelling. In contrast, it appears that diabetes on top of essential hypertension is associated with media hypertrophy, without a reduction of lumen diameter as measured in passive conditions.[65,66] The same hypertrophy was also shown by one of these studies[66] in normotensive diabetics, supporting a pressure-independent effect of diabetes on resistance vessel morphology.[23]

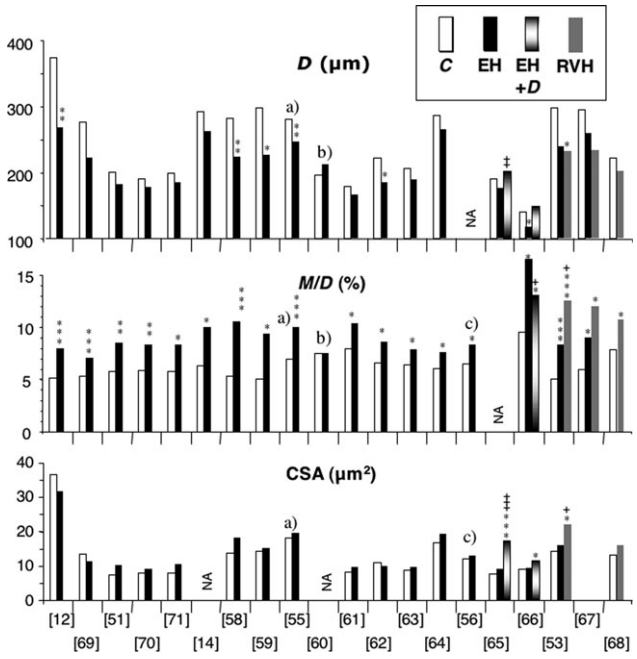

Figure 5 Morphologic characteristics of small subcutaneous arteries in untreated hypertensive patients vs. normotensive human subjects. Studies examined vessels isolated from biopsy material, using either the pressure myograph or the wire myograph. *D* internal diameter. *M/D* ratio of media thickness to internal diameter. CSA, cross-sectional area. *C*, normotensive controls. EH, untreated essential hypertension. EH+D, essential hypertension and diabetes; RVH, renovascular hypertension. NA, data not available from original publication. Data are the mean values reported in the various studies (references in square brackets). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs. *C*. $^{+}P < 0.05$, $^{++}P < 0.01$, $^{+++}P < 0.001$ vs. EH. Notes: a) Means and *P*-values recomputed by pooling the two EH groups reported separately in the original publication. b) Group EH consisted of normotensive offspring of hypertensive parents. c) The largest study, comprising 59 controls and 159 non-diabetic patients with essential hypertension.

Finally, the limited data available suggest that, contrary to the essential form, hypertension secondary to renovascular disease could promote media growth in human small subcutaneous arteries.[53,67,68]

There are at least two caveats regarding the interpretation of these clinical data. First, the extent to which they might be contaminated by the aforementioned sampling problem is impossible to assess. Second, the subcutaneous vasculature is not necessarily representative of other vascular beds. There are a few observations to mitigate the latter concern. We may recall here the evidence of eutrophic remodelling in the intestinal microcirculation of hypertensive patients presented by Short.[28] In addition, a positive correlation has been found in hypertensive patients between coronary flow reserve and the *M/D* ratio of subcutaneous arteries, indeed supporting that hypertensive changes of microvascular structure were not limited to the subcutis.[72] Finally, Harazny *et al.*[73] have very recently been able to evaluate the *W/D* ratio of retinal arterioles in patients with treated hypertension and without advanced retinopathy (stages III or IV). To that effect, they used laser Doppler imaging whereby outer and inner diameters were respectively determined from reflection and perfusion images. Results indicated a higher ratio when blood pressure control was poor than when it was satisfactory.

4. Mechanisms of altered resistance vessel structure in hypertension

It is thought that hypertensive remodelling of resistance vessels results from complex, yet incompletely understood interactions between genetic factors, intrinsic adaptation of vascular wall to altered mechanical conditions, and neurohumoral as well as local trophic influences.[9]

4.1 Genetic factors

Considering the polygenic nature of essential hypertension, it would be consistent that particular traits would exist that would favour alterations of vascular structure. Some evidence along this line is given by comparison of the same vessels in different strains of genetically hypertensive animals. Specifically, medial hypertrophy of large mesenteric arteries seems much more marked in mRen-2 transgenic rats than in age-matched SHRs.[36] Another way to search for 'remodelling traits' is to examine the ontogeny of microvascular structure in genetic hypertension. Results have been heterogeneous. A structural reduction of lumen diameter has been detected in the small mesenteric arteries of young SHRs, when their blood pressure did not yet differ from that of age-matched WKY controls[74] but normal structure of these same vessels has been reported in mRen-2 transgenic rats at the prehypertensive stage.[39] Regarding human data, forearm Rmin was higher in young normotensive subjects with than without a family history of essential hypertension.[75,76] In neither study however was it clear that structural changes antedated hypertension, because blood pressure, although in the normotensive range, was somewhat higher in the offsprings of hypertensive parents. In a similar group of subjects, subcutaneous small arteries failed to demonstrate any structural abnormality when examined with wire myography (*Figure 5*).[60] The view that essential hypertension could be initiated by a primary, genetically determined remodelling of resistance vessels is now largely abandoned.

4.2 Pressure-dependent factors

Structural narrowing of resistance vessels occurs in all likelihood posterior to the onset of essential hypertension, although possibly prior to left ventricular hypertrophy or any other end-organ damage.[71] Posteriority is furthermore self-evident in case of secondary hypertension. In addition, the evidence for a causal pathway leading from high blood pressure to microvascular remodelling is fairly strong. In the early 70s, Folkow *et al.*[77] reported that the abnormal elevation of hindquarter Rmin seen in adult SHR was abolished by prior partial ligation of the abdominal aorta below the renal arteries carried out at the pre-hypertensive stage, an intervention that protected the lower limb vessels from exposure to high blood pressure. Also in pre-hypertensive SHRs, Bund *et al.*[78] partially ligated the left external iliac artery, let the animals develop hypertension, and then observed with wire myography that distal femoral arteries excised from the right leg (unprotected) showed hypertrophic remodelling in comparison with those taken from the left leg (protected). Similar evidence exists with models of secondary hypertension.[40,79]

We have previously reviewed the general tendency of chronic hypertension to produce media growth in larger as

opposed to inward eutrophic remodelling in smaller resistance vessels. It is believed that this pattern may be explained by the general mechanisms that regulate wall stress (σ) in blood vessels.[1,42,80] By virtue of the Laplace law, the same acute elevation of transmural pressure produces a greater increase of σ in larger arteries, due to their smaller *W/D* ratio in comparison with more distal narrower vessels. Furthermore, the larger vessels have a very limited, or even no myogenic response, so that their only way to regulate σ in the face of persistent distension is to increase wall thickness, by way of a growth response. In contrast, smaller vessels have vigorous myogenic tone, which together with a larger *M/D* ratio allows them to control σ in the short term by mere active variations of lumen size and wall thickness. If the elevation of transmural pressure persists, myogenic constriction progressively gives way to structural rearrangement of wall material around a smaller lumen, i.e. the pattern of inward eutrophic remodelling.[81,82] The aforementioned greater hypertrophy and lesser eutrophic remodelling of resistance vessels in hypertensive diabetics[65,66] may be understood in this context, because diabetes impairs myogenic tone.[66]

A final remark relates to the differential effects on vascular biology of pulsatile vs. steady mechanical forces.[83] In rabbit aorta for example, pulsatile variations of transmural pressure did not trigger the same intracellular signalling events [interestingly related to activation of kinases associated with focal adhesion (FA) points, see below] as did a steady increase of this variable.[84] It is now realized that pulsatile pressure and flow penetrate much deeper into microvascular networks than previously thought,[16] and we may thus speculate that hypertensive resistance vessels may not be exposed to the same pulsatile stress/strain than are normotensive ones. Whether this factor contributes to remodelling could become an active area for future research.

4.3 Pressure-independent factors

In hypertensive models, the strategy of protecting a specific vascular bed from high blood pressure in order to sort out pressure-mediated from non-pressure mediated mechanisms of remodelling has in fact yielded some contradictory results.[79,85,86] The most cited evidence for the importance of pressure-independent factors in hypertensive remodelling of resistance vessel has been obtained in rats receiving a low-rate infusion of angiotensin II. In such conditions, blood pressure remains initially normal, and then slowly increases over several days, after which media hypertrophy of small mesenteric arteries is observed. Co-treatment of these animals with an infusion of hydralazine completely prevented hypertension, but had no effect on the development of vascular hypertrophy.[44]

In the following, we shall briefly discuss relevant neurohumoral as well as local non-mechanical factors. These might act independent of pressure, interact with pressure-dependent mechanisms, or constitute essential mediators thereof, with the current state of knowledge not allowing to fully distinguishing between these possibilities.

4.4 Sympatho-adrenergic system

Sympathetic activation is a hallmark of human essential hypertension, and plays a well-known, in part pressure-independent role in the development of left ventricular hypertrophy. A trophic impact of adrenergic stimulation on vascular smooth muscle has also been demonstrated *in vitro*. For example, stimulation of α1 adrenoreceptors enhanced the production of extracellular matrix (ECM) and the expression of transforming growth factor β (TGF-β) by cultures of primary human aortic smooth muscle cells, while β1 stimulation had the opposite effects.[87] The recent suggestion of a role for dysregulated production of TGF-β in hypertensive structural narrowing of resistance vessels must be noted here.[88]

On the other hand, there are no conclusive data, whether from animal models or clinical studies, to support an independent role of sympathetic activation in the pathogenesis of hypertensive remodelling of resistance vessels (for review, see[22]). In adult SHRs who underwent neonatal sympathectomy plus ablation of the adrenal medulla at 4 weeks, vascular structure was normal, but so was blood pressure.[89] In Sprague-Dawley rats made hypertensive with a slow low dose infusion of angiotensin II, neonatal sympathectomy+medullectomy influenced neither the time-course of blood pressure, nor the development of medial hypertrophy in small mesenteric arteries.[90] In the clinical arena, the structure of small subcutaneous arteries did not differ between patients with a hyperactivated sympatho-adrenergic system due to pheochromocytoma and patients with essential hypertension.[91] β-blockers have consistently failed to influence the structure of these arteries in essential hypertensive patients (see below).

4.5 Angiotensin II

Beyond contraction of smooth muscle, angiotensin II has the ability to promote many processes in cardiovascular tissue, including cell growth, migration, differentiation, and apoptosis, as well as modulation of ECM composition and turnover. For these reasons, angiotensin II is a likely candidate for a pivotal role in remodelling throughout the cardiovascular system.[92] Interestingly, the growth-promoting properties of angiotensin II have been demonstrated at physiological concentrations (10^{-10} M)[93] in cultures of primary smooth muscle cells obtained from human small subcutaneous arteries.[94] In this respect, cells from patients with essential hypertension were more sensitive than cells from normotensive controls.[94] The aforementioned results with slow low-dose infusion of angiotensin II in the rat have convincingly implicated this peptide as a primary, pressure-independent mediator of small mesenteric artery medial hypertrophy in this model.[44] It has been speculated that angiotensin II may participate in inward eutrophic remodelling by differentially favouring growth on the luminal side and apoptosis on the abluminal side of vascular wall.[95]

4.6 Reactive oxygen species

It is now well accepted that vascular production of reactive oxygen species (ROS) is abnormally high in hypertension.[96] ROS in turn may trigger many cellular events, including growth. For example, the angiotensin II-induced growth of rat aortic smooth muscle cells was suppressed either by treatment with diethyldithiocarbamate, as ROS scavenger, or by overexpression in these cells of superoxide dismutase, an antioxydant enzyme.[97] On *in vitro* administration of

angiotensin II, SMCs isolated from human small subcutaneous arteries also had a ROS-mediated growth response, which very interestingly was more marked in cells from hypertensive than from normotensive subjects.[98]

4.7 Nitric oxide

A low bioavailability of nitric oxide (NO), linked to endothelial dysfunction and possibly mediated in part by excess ROS, seems widely implicated at multiple levels in the pathogenesis of hypertension.[99] NO has myriads of biological effects, among which a negative control exerted on cellular growth. Mice with deletion of the gene coding for the endothelial form of nitric oxide synthase (eNOS) are mildly hypertensive. In these mice, the inward hypotrophic remodelling of conduit arteries, which normally follows a chronic reduction in blood flow, is replaced by a hyperplastic response.[100] Hypertrophic remodelling of small coronary arteries has been observed in rats made hypertensive by the chronic administration of NG-methyl-l-arginine, an inhibitor of NOS, and this structural abnormality was not reversed when blood pressure was normalized by concomitant treatment with hydralazine,[45] suggesting that suppression of NO could enhance vascular growth in a pressure-independent manner. Interestingly, a simulation carried out with the aforementioned computational model of rat mesenteric microcirculation by Pries *et al.*[27] suggested that even minor degrees of endothelial dysfunction can powerfully potentiate the impact of hypertension on microvascular structure. In hypertensive humans, endothelial dysfunction of the microvasculature has been demonstrated in the skin.[101]

4.8 The extracellular matrix—integrin—cytoskeleton axis

Integrins are ubiquitous dimeric transmembrane receptors which ligate specific sites of various ECM proteins, for example fibronectin and collagens.[80,102,103] Their cytoplasmic part binds cytoskeletal proteins such as actin. Within the cell membrane, ligated integrin complexes occur in clusters called FA points. This arrangement allows for a tight mechanical connexion between ECM and cytoskeleton. FAs also comprise a complex signalling apparatus, able to influence all major cell functions, including cell cycle, gene expression, substrate adhesion, motility, and membrane ion channel permeability. In a multicellular environment, any change in cell number, shape, or position requires the active participation and dynamic restructuring of the ECM–integrin–cytoskeleton axis. This axis is the major mean that cells have to sense their mechanical environment and react accordingly. For example, it has been shown that the $\alpha_V\beta_3$ and $\alpha_5\beta_1$ integrins are the stretch sensors responsible for initiating myogenic contraction in resistance vessels.[104]

With this background, it seems logical that the ECM–integrin–cytoskeleton axis should be profoundly implicated in hypertensive remodelling of resistance vessels. Rat mesenteric arteries were pressurized *in vitro* and exposed to endothelin-1 for 3 days; eutrophic remodelling ensued an effect blocked by an antibody directed against the β_3 integrin subunit.[105] In eutrophically remodelled small mesenteric arteries of hypertensive mRen-2 transgenic rats, expression of the α_V integrin subunit was increased, in comparison with similar vessels from normotensive controls.[39] In that study furthermore, some mRen-2 rats received at the pre-hypertensive stage a peptide antagonist of α_V: this treatment had no effect on the further time course of blood pressure, but modified the remodelling of mesenteric arteries from mainly eutrophic to mainly hypertrophic.

4.9 Adventitial cells

The vascular adventitia has traditionally been considered as a passive supportive structure. There is mounting evidence that it also actively participates in general remodelling processes.[106] In rat carotid artery subjected to balloon injury, adventitial fibroblasts differentiated to myofibroblasts and migrated through the media to participate in the formation of neointima.[107] In rats with hypertension secondary to chronic pharmacologic inhibition of NOS, the basilar artery was eutrophically remodelled, and its adventitial layer revealed a greatly increased cellular density.[108] Eutrophically remodelled mesenteric arteries of SPSHRs also had abnormally dense adventitial cellularity, and in addition displayed a striking number of advential-looking cells in the media.[109] Considering the potential role of sympathetic activation evoked above, it is relevant that adventitial fibroblasts highly express α1-adrenergic receptors, and that noradrenaline can stimulate their proliferation and differentiation to myofibroblasts, at least *in vitro*.[110]

5. Effects of antihypertensive drug treatment on the structure of resistance arteries

This topic was systematically reviewed by Christensen and Mulvany[111] in 2001. Thirty clinical studies were identified where resistance vessel structure was evaluated before and after blood pressure lowering with antihypertensive medication. All major classes of drugs were tested, over periods ranging from 1 to 84 months, in all cases with substantial improvement of blood pressure control. Twenty-one studies inferred structure from the measurement of Rmin with forearm plethysmography and the remaining 9 used myography of biopsied small subcutaneous arteries. It came out quite clearly that at least partial reversal of hypertensive structural changes could be obtained with all drug classes, except with β-blockers. As shown in *Table 1*, more recent studies of biopsied subcutaneous arteries have mostly borne out this conclusion. Very recently, Mathiassen *et al.*[112] presented data in 28 patients with essential hypertension. In these subjects, forearm Rmin had remained unchanged and abnormally high despite excellent blood pressure control obtained with a β-blocker for one full year. For the next year, medication was switched to an AT1 antagonist (eprosartan), a period during which blood pressure remained stable while Rmin decreased by 16% ($P < 0.01$).

The blatant inability of β-blockers to affect the structure of resistance vessels has been attributed to their mode of action through reduction of cardiac output rather than vasodilation.[111,112] Considering our previous discussion on mechanisms, it is also possible that vasodilator antihypertensive drugs, especially those interfering with the renin-angiotensin system, influence vascular structure by mechanisms independent of haemodynamic factors, but this issue is completely unsolved at present.

Table 1 Effect of antihypertensive treatment on blood pressure and on resistance artery structure

Primary drug	Drug type	%change MBP	%change *M/D*	Treatment duration (months)	Reference
Amlodipine	CaB	−8%**	39%*	12	116[a]
Atenolol	β+	−11%	7%	12	117
Atenolol	β+	−18%***	0%	12	115
Perindopril	ACE	−17%***	−15%*	12	115
Losartan	ARB	−10%**	−15%*	12	116[a]
Candesartan	ARB	−7%*	−16%**	12	118
Valsartan	ARB	−13%*	−19%*	12	117
Enalapril	ACE	−13%*	−21%**	12	118
Irbesartan	ARB	0%	−23%**	12	119[b]

Recent clinical studies which documented changes in mean blood pressure (MBP) and in media/lumen ratio (*M/D*) of small subcutaneous arteries following antihypertensive treatment. Calcium antagonists (CaB), β+ antagonist of beta-adrenergic receptors, ACE inhibitors of the angiotensin-converting enzyme, ARB antagonist of the AT1 angiotensin receptor.

[a]One study reporting the *M/D* ratio of vessels <100 μm, measured with histology of skin biopsies.[116] In all others, 200–300 μm arteries were mounted in a wire[115,118] or pressure[117,119] myograph.

[b]One study in which patients whose blood pressure was well controlled with a β-blocker were crossed-over to an ARB.[119]

*$P < 0.05$.

**$P < 0.01$.

***$P < 0.001$.

6. Prognostic implication of hypertensive resistance vessel remodelling

We now have three relevant and concordant clinical studies. The first one was published in 2003 by Rizzoni *et al*. Within an 8-year period, 128 patients with either essential or secondary hypertension had had a gluteal or omental fat biopsy after being weaned from antihypertensive medication for at least 3 weeks. Follow-up ensued for a mean duration of 5 years (range 2.6–9.9), with a composite endpoint of various major and minor cardiovascular events, which occurred in 33 cases. On multivariable analysis, a high *M/D* ratio of the small artery and a high pulse pressure were the only independent predictors for event occurrence. A few years later, the authors extended their survey as follow-up included more subjects. The expanded cohort comprised 303 patients observed for a mean duration of 6.9 years (range 0.6–13.9). It was thus possible to distinguish major (sudden death, stroke, myocardial infarction, $n = 25$) from other cardiovascular events ($n = 23$). Here, a high *M/D* ratio was an independent predictor for the occurrence, not only of any event as before, but also of any major one.[57] Both studies contained a mix of diabetic and non-diabetic hypertensive patients, which may be seen as a weak point considering the possible independent impact of diabetes on small artery morphology (see above). However, Mulvany's group reported essentially the same results in a more homogeneous cohort of 159 non-diabetic subjects with essential hypertension (mean follow up time 10 years, composite outcome of cardiac, cerebrovascular, renal, and peripheral arterial events, 30 events in total).[56]

In view of these data, should evaluation of small artery structure become part of clinical evaluation in hypertensive disease? In the present state of knowledge, probably not, if only because biopsies of subcutaneous arteries are not practical on a large scale.[113] The aforementioned non-invasive structural assessment of retinal arterioles[73] might seem in that respect a promising approach, which deserves further evaluation.[113]

7. In form of conclusion: Should we aim to correct resistance vessel structure when treating hypertension?

At the time of writing the present review, this issue has not been resolved. The answer could come from two different types of considerations. First, does remodelling of resistance vessels participate in hypertensive organ damage? Second, does this remodelling hamper the proper control of blood pressure?

The possible involvement of resistance vessel remodelling in hypertensive end-organ damage has received the greatest attention in the case of the myocardium.[72,114,115] Notably, in patients with essential hypertension, coronary flow reserve improved concomitantly with normalization of small subcutaneous artery structure following 1 year of treatment with perindopril, an ACE inhibitor. In contrast, coronary flow reserve worsened, and small subcutaneous artery structure remained unchanged in a parallel group in whom the same level of blood pressure reduction was achieved over the same period, by the β-blocker atenonol.[115] In that study, interestingly, myocardial blood flow was measured with position emission tomography, allowing expression of flow per unit mass of tissue, thus removing at least in part the influence of left ventricular hypertrophy (which regressed with the ACE inhibitor only). Assuming a correlation between the remodelling of subcutaneous and intramyocardial resistance arteries, as suggested by another clinical study,[72] correction of this anomaly would contribute to improve the functional status of the coronary circulation.

That altered vascular structure could hamper the therapeutic control of blood pressure would be suggested by an oversimplified version of the Folkowian view—i.e. high blood pressure breeding remodelling which in turn breeds high blood pressure. However, Folkow[9] himself has stressed that this positive feed-back loop would be unsustainable without intervention of powerful counter-regulatory mechanisms, the nature of which remains incompletely understood. As also underscored by Mulvany,[21] the control of blood pressure involves: (i) one or several setpoints for

this variable, (ii) fast processes (i.e modulation of vessel tone through local and neurohumoral mechanisms) to keep blood pressure closest to this (these) setpoint(s), and (iii) slow processes (remodelling) which allow adaptation to a sustained setpoint change, in energetically economical terms (i.e. reduced lumen diameter at normal activation level of smooth muscle in resistance vessels). What determines the setpoint(s) is presently unknown, although the need to maintain appropriate blood and oxygen supply to various organs, notably the kidney, is probably involved.[21] In the hypertensive circulation, correcting the structure without also changing the setpoint would only activate neurohumoral and other mechanisms to keep blood pressure high. Consistent with these considerations, we have noted above a marked dissociation between the impacts of antihypertensive therapy on blood pressure and on resistance vessel structure (*Table 1*).[111] If and how the various drug classes affect the setpoint for blood pressure might become a focus of future research.

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