Small Artery Remodeling and Significance in the Development of Hypertension

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The structure of the resistance vessels is altered (remodeled) in individuals with high blood pressure (essential hypertension). The structure is dependent not only on blood pressure but also on blood flow and hormonal environment. Vascular biology is providing increased knowledge of the mechanisms involved and thus contributing to our understanding of the pathophysiology of the disease.

Up to 20% of individuals living in developed countries have elevations of blood pressure, which is associated with increased risk of cardiovascular morbidity and mortality. World wide, it is suggested that at least 500 million persons have or will have abnormally elevated blood pressure. Drug therapy is usually able to correct the pressure and is also successful in reducing, or even correcting, the risk of cardiovascular events. However, despite this major pharmacotherapeutic success, the cause of increased blood pressure in most cases remains unknown, and the condition is termed essential hypertension.

Despite this lack of knowledge concerning the pathogenesis of essential hypertension, there are many clues. There is the observation that children of hypertensive parents have increased risk of themselves becoming hypertensive, to the extent that 50% of the incidence is thought to be genetically based. There is also evidence that the environment or diet plays a role, since it is observed, mainly in developing countries, that on moving from villages to towns people have increased risk of developing hypertension. A third clue is evidence that a renal defect may be responsible, with the finding (mainly from animal studies) that renal transplants from a hypertensive to a normotensive individual results in the latter individual becoming hypertensive.

Investigations of the cause of hypertension are complicated by the general finding that most parameters are on average normal, e.g., sympathetic activity and plasma renin activity. There is, however, one parameter that is consistently abnormal: an increased peripheral resistance. The peripheral resistance is determined mainly by the distal part of the arterial vasculature (the resistance vessels), consisting of the small arteries (arteries with diameter <300 μm) and the arterioles (the arteries leading into the capillaries) (7). Current evidence (13) indicates that the increased peripheral resistance is due in part to a general narrowing of all resistance vessels and in part to a reduction in the number of parallel-connected arterioles, a process known as rarefaction. In principle, the narrowing of the resistance vessels could be due to altered function (an increased degree of vascular tone, due either to increased neurohormonal drive or to altered vascular sensitivity). However, the evidence for this is weak, with the exception of evidence from a number of groups for decreased endothelial function. In contrast, as discussed below, the evidence that the increased resistance is due to structural changes (known as remodeling) in the resistance vessels is much stronger (10).

This brief review will summarize current concepts concerning the structure of the small arteries, as a subgroup of the resistance vessels, and the remodeling that is seen in essential hypertension. We show that the available evidence points to important roles for blood flow and growth factors, in addition to blood pressure, as causes of resistance artery remodeling. This has important consequences in regard to optimal treatment of hypertension. The relation between vascular structure and blood pressure is discussed, with particular reference to the structure of renal resistance vessels, for which there is evidence that these play a key role in the development of hypertension. Finally, there is an outline of recent work concerning the cellular mechanisms involved in the remodeling process.

Small artery structure

Small arteries consist classically of three layers: intima, media, and adventitia. The longitudinally arranged endothelial cells of the intima are separated from the circumferentially arranged smooth muscle cells and connective tissue of the media by an internal elastic lamina. The adventitia contains many components, including, in most cases, sympathetic nerves, considerable amounts of collagen, and fibroblasts. The primary functional characteristic of the vessel is the lumen diameter, which determines their resistance (to the fourth power according to the Poiseuille relation); this characteristic is determined by the active and structural properties of the vessel. The active properties of a vessel are determined by the state of contraction of the individual smooth muscle cells, their number, and their arrangement. The structural properties of a vessel (lumen diameter, media thickness, and wall thickness, and hence the physiologically important media:lumen and wall:lumen ratios) are determined with the smooth muscle cells relaxed and usually with the vessels exposed to a given intravascular pressure.

Remodeling in human hypertension

Early animal studies demonstrated that hypertension was associated with a remodeling of the resistance vessels, and
those findings have been strongly supported by more recent studies using human material. In the human studies, small arteries have been dissected out from gluteal skin biopsies, taken under local anesthesia, and mounted on myographs (1). The studies have uniformly shown (13) that essential hypertension is associated with a reduced lumen and increased media:lumen ratio in resistance vessels. In particular, this work has shown that the altered morphology is not associated with any increase in the media cross-sectional area. Furthermore, the size of the individual smooth muscle cells within the media is also normal, whereas the functional responses of the smooth muscle are little affected. There is thus a rearrangement of otherwise normal cells around a smaller diameter. This form of remodeling is known as “eutrophic” (Fig. 1, left), i.e., no change in amount of material, in contrast to forms associated with increased (“hypertrophic”) or decreased (“hypotrophic”) amounts of material.

Antihypertensive treatment and resistance vessel remodeling

Although the structural changes in the resistance vessels are often considered the hallmark of hypertension, it has been repeatedly shown that otherwise effective antihypertensive treatment is not necessarily able to correct the abnormal small artery structure seen in hypertension (Fig. 1, right) (14, 15, 18), raising the question of whether such correction is needed. However, it is likely that vascular structure is of importance as regards the vascular reserve (the ability to increase blood flow with maximal vasodilatation), in that reduction of blood pressure without correction of resistance vessel structure will reduce the vascular reserve. Thus the decreased coronary vascular reserve seen in essential hypertension will be exacerbated rather than relieved (17), suggesting that correction of vascular structure should in principle be an important goal of antihypertensive treatment. However, the prognostic consequences of this are still not clarified.

Determinants of remodeling

The apparent discrepancies between resistance vessel structure and blood pressure are likely due to the fact that vascular structure is not only dependent on pressure but also on the flow through them and the hormonal environment. Thus the structure of blood vessels is not constant but is continually being adjusted to allow them to fulfill their function of delivering blood to the capillaries in the correct quantity and at the correct pressure. The remodeling seen in essential hypertension and during antihypertensive treatment therefore needs to be explained in terms of these initiating factors.

A scheme for how pressure, flow, and hormones can initiate vascular remodeling is presented in Fig. 2. Intravascular pressure causes an increase in the wall stress, which then stimulates a hypertrophic process leading to an increase in wall thickness (9). However, the flow through a vessel also has a profound effect on the vascular structure: increases in flow lead to increases in diameter and in wall thickness (5). Here, the increased diameter is initially due to functional vasodilatation due to the release of vasodilating substances from the endothelium. The vasodilatation, however, also causes (according to the Laplace relation: wall tension = pressure × radius) an increase in wall stress, leading to a structurally based increase in diameter and again to increase in wall thickness. Hypertrophic processes are also thought to be initiated through growth factors, including angiotensin II (AII). It remains unclear whether these hypertrophic processes are due to proliferation (increased number of cells) or increased size of cells, although flow-induced remodeling has recently been shown to be associated with proliferation and dedifferentiation (5).

As indicated above, essential hypertension appears to be associated with eutrophic, not hypertrophic, remodeling of the small arteries. The factors causing eutrophic remodeling are not known, but the following process is suggested: increased neurohumoral activity leads to vasoconstriction and increased blood pressure. On the basis of the Laplace relation, the decrease in diameter (and resulting increase in wall thickness) will ensure that the wall stress remains normal, thus eliminating a hypertrophic response. In time, it is suggested, the active vasoconstriction changes to a passive remodeling, as has recently been demonstrated in vitro (3).
The lack of effect of certain forms of antihypertensive treatment, notably those (like β-adrenoceptor antagonists) that act more by reducing cardiac output than by reducing peripheral resistance, can be accounted for in terms of the concepts outlined in Fig. 2. Thus if antihypertensive treatment through a reduction in cardiac output reduces flow through the resistance vessels, this can cause a structurally mediated reduction in diameter, which can counteract the structural effects of a fall in blood pressure. On the other hand, if the treatment causes a vasodilatation (directly or indirectly), flow will not be reduced, and the beneficial effects of lowered blood pressure on small artery structure will be seen. On this basis, it may be expected that a correction of vascular structure is more a function of changes in resting peripheral resistance rather than blood pressure. This is supported by the available literature, which shows that vasodilator treatment, but not treatments that cause reduction in cardiac output, are effective in correcting resistance vessel structure, as inferred from reduction in minimum vascular resistance (8). These in vivo observations are consistent with the in vitro data mentioned above, in which angiotensin-converting enzyme inhibitors (which cause vasodilatation) correct resistance vessels, whereas beta blockers (reducers of cardiac output) do not, both in humans (Fig. 1) (15, 18) and in animal models (6).

Small artery structure and blood pressure

In principle, according to the Laplace relation, a structurally mediated increase in the wall:lumen ratio of resistance vessels will in itself be a form for activation leading to increased peripheral resistance (9). Thus an increased wall:lumen ratio might be a factor in sustaining an established hypertension. On the other hand, as indicated above, there are situations in which blood pressure is reduced with unaltered vascular structure, suggesting that other factors such as flow and hormonal environment play a role. A simple framework for understanding the relation between vascular structure and blood pressure is shown in Fig. 3. The starting point is the suggestion of Julius (11) that the cardiovascular system apparently seeks to keep the blood pressure at a "required blood pressure," as determined by the various functions of the body. Then if, for example, the pressure is too low, a signal is sent to increase the neurohumoral drive. The effect of this signal on the lumen is dependent on both its strength and the actual resistance vessel structure (for example wall:lumen ratio). The resulting increase in the peripheral resistance then, together with the cardiac output, increases the pressure, the process continuing until the pressure equals the required pressure. This is a fast process, a negative feedback mechanism, and inherently stable.

In addition to these fast processes, the model has slow processes, so that in the long term as indicated above the vascular structure can be altered by 1) the pressure, 2) the flow, and 3) neurohumoral influences. Thus if for some reason the required pressure increases, there will initially be an increase in the neurohumoral drive, and the fast process will result in the pressure rising. But then the slow processes will ensue, with an increase in resistance vessel wall:lumen ratio, due both to the increased neurohumoral drive and to the increased pressure. With the increase in resistance vessel wall:lumen ratio, the neurohumoral drive necessary to maintain the increased blood pressure will be reduced. Thus in the long run, the increased pressure will be maintained by a normal neurohumoral drive but with an increased wall:lumen ratio (9), in other words, the situation normally seen in essential hypertension.

The schematic emphasizes that small artery structure is not alone determined by the prevailing blood pressure and furthermore that small artery structure does not in itself determine blood pressure. Rather, small arteries should be considered as effector organs of neurohumoral drive, where for example an increase in the wall:lumen ratio can amplify the effects of this drive.

Role of renal afferent arterioles in the pathogenesis of hypertension

Although the scheme in Fig. 3 suggests that vascular structure is not a controller of blood pressure, there is one group of resistance vessels, the renal afferent arterioles, for which there is quite good evidence that they play a primary role in the pathogenesis of hypertension. As regards humans, the evidence is not rigorous, but as regards certain animal models of hypertension, in particular the so-called spontaneously hypertensive rat (SHR), the evidence seems clear.

The SHR is a genetic model of essential hypertension, having been bred through selective selection for having a high blood pressure. The increased blood pressure develops over the first 12 wk. Classic work (2) has shown that, in young SHR, although the blood pressure is still within normal limits, the renal vascular resistance is substantially increased and the renal blood flow and glomerular filtration rate are decreased. These abnormalities are associated with a structurally mediated narrowing of the vessels immediately proximal to the glomeruli, the renal afferent arterioles. By the age of 12 wk, when the high blood pressure is established, the renal vascular resistance remains increased and the renal afferent arterioles continue to be narrowed, but the renal blood flow and glomerular filtration rate are normalized. It was therefore suggested that the rise in blood pressure was a homeostatic process to overcome the structural abnormality of the renal vasculature and restore the water and salt balance of the body according to the principles of Guyton (2). Thus a structurally mediated narrowing of the renal afferent arterioles is seen as
playing a primary role in the pathogenesis of hypertension in this model.

The hypothesis was tested in our laboratory by using F2-SHR/WKY animals [SHR were crossed with normotensive Wistar-Kyoto rats (WKY) to produce F1-SHR/WKY, which in turn were crossed to produce F2-SHR/WKY]. All of the F2-SHR/WKY remain normotensive until ~7 wk of age, whereafter some develop hypertension and some remain normotensive. In our experiment, the diameter of renal afferent arterioles was measured at 7 wk by using a histological method that necessitated unilateral nephrectomy. The rats were then followed until 23 wk of age, at which time it was found that those rats that had narrow afferent arterioles at 7 wk were the rats that developed hypertension. The rats with wide afferent arterioles showed little change in blood pressure. Thus, in this model at least, a narrowed renal afferent arteriole at a young age is a predictor of later development of high blood pressure. Furthermore, treatment of young SHR (with angiotensin-converting enzyme inhibitors) causes a large, structurally mediated dilation of the renal afferent arterioles and permanently reduces pressure, even after treatment is withdrawn. Thus abnormal renal afferent arteriolar structure forms part of a chain leading to hypertension in the SHR. Whether this is the case for essential hypertension is not known, but offspring of parents with essential hypertension do have increased renal vascular resistance at an early age. These findings have been recently reviewed (16).

**Signaling pathways**

The cellular mechanisms involved in vascular remodeling are currently the object of intensive investigation (4, 19). At present, most information comes from cell culture experiments, in some cases using smooth muscle cells derived from human small arteries. However, although cell culture experiments have provided much information about All-mediated mechanisms, information about pressure-mediated mechanisms can only be obtained from intact vessels (cannulated and pressurized), and it is only recently that such experiments have been performed (12, 20). Here there has been focus on the phosphorylation of extracellular signal-regulated kinase 1 and 2 (ERK1/2) and mRNA expression of the protooncogenes c-fos and c-myc, as well as the role of the platelet-derived growth factor (PDGF)-β receptor, all of which have been shown to play important roles in growth processes in vascular smooth muscle cell cultures (4, 19).

The studies with intact vessels have shown (see Ref. 13) that indeed ERK1/2 is a key enzyme in mediation of responses to All and to pressure, and it appears that they are mediated by so-called c-Src tyrosine kinase in activation of ERK1/2. Furthermore, using specific inhibitors of the PDGF-β receptor tyrosine kinase and of the receptor itself, the PDGF-β receptor has been found to play a major role in mediating the effects of mechanical stress and All on ERK1/2 activation (see Ref. 13). It has been suggested that the interaction between the All receptor and the PDGF-β receptor is through transactivation (4).

On the basis of the above studies, as well as on cell culture experiments, Fig. 4 summarizes, in a simplified manner, current ideas as to how mechanical stress and All can initiate growth processes in resistance arteries. Activation of the PDGF-β receptor is seen as a central feature of pressure and All activation of remodeling processes as follows: mechanical stress leads, via integrins, focal adhesion kinase, and c-Src (a tyrosine kinase), to activation of the PDGF-β receptor. Pressure...
leads also to the release/synthesis of All. This acts on the All receptor through phospholipase C, activating protein kinase C and raising the cytoplasmic calcium. Protein kinase C activation leads to activation of the Ras-Raf pathway, activation of ERK kinase, and thus ERK1/2 activation. In addition, both pressure and All lead to activation of the PDGF-β receptor, either through autocrine release/synthesis of PDGF or through trans-activation of the PDGF-β receptor. Activation of ERK1/2 leads through activation of transcription factors to activation of proto-oncogenes like c-fos and c-myc and proliferation and protein synthesis. Here, expression of matrix metalloproteinases (MMPs), such as MMP2 and MMP9, are thought to play central roles in the remodeling processes. Whether the central role of the PDGF-β receptor is because it forms part of a linear signal pathway or whether the effect of the PDGF-β receptor on ERK1/2 requires a synergy between its own intrinsic activity together with All receptor activity and mechanical loading remains to be determined.

**Conclusions**

Remodeling of the resistance vasculature plays a key role in the pathogenesis of essential hypertension, in which eutrophic remodeling allows the vessels to maintain an increased resistance without increased activation. The available evidence shows that correction of the hypertension-related abnormal small artery structure requires not only correction of blood pressure but also of flow. A primary role for abnormal structure of the renal afferent arterioles causing hypertension in animal models has been identified. The mechanisms involved are still not clear, but at the cellular level, there is growing evidence that the PDGF-β receptor and ERK1/2 play pivotal roles.

**References**


