Structure and Mechanical Properties of Resistance Arteries in Hypertension
Role of Adhesion Molecules and Extracellular Matrix Determinants

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Abstract—Abnormalities of resistance arteries may play a role in the pathogenesis and pathophysiology of hypertension in experimental animals and humans. Vessels that, when relaxed, measure <400 μm in lumen diameter act as the major site of vascular resistance and include a network of small arteries (lumen ~100 to 400 μm) and arterioles (<100 μm). Because increased peripheral resistance is generated by a narrowed lumen diameter, significant effort has been focused on determining the mechanisms that reduce lumen size. Three important vascular components are clearly involved, including alterations of vascular structure, mechanics (stiffness), and function. Structural abnormalities comprise a reduced lumen diameter and thickening of the vascular media, resulting in an increased media-lumen ratio. Changes in the mechanical properties of an artery, particularly increased stiffness, may also result in a reduced lumen diameter. These vascular abnormalities may be caused or influenced by the expression and/or topographic localization of extracellular matrix components, such as collagen and elastin, and by changes in cell-extracellular fibrillar attachment sites, such as adhesion molecules like integrins. This article discusses the abnormalities of resistance arteries in hypertension and reviews the evidence suggesting an important role for adhesive and extracellular matrix determinants. (Hypertension. 2000;36:312-318.)

Key Words: remodeling ■ resistance ■ elasticity ■ integrins ■ hypertension, essential

Essential hypertension is associated with increased peripheral vascular resistance to blood flow.1 Resistance arteries are vessels with lumen diameters measuring <400 μm when relaxed, and they constitute the major site of generation of vascular resistance.2 These vessels include small arteries, with relaxed passive lumens of more than ~100 μm (values vary between authors), and arterioles, which are smaller. A significant role has been proposed for small arteries in the pathogenesis of hypertension3 and its outcomes.4 The fundamental cause of increased peripheral resistance is a decrease in lumen diameter. According to Poiseuille’s law, resistance varies inversely with the fourth power of the blood vessel radius, so that a small decrease in the lumen markedly increases resistance.

In hypertension, the vascular changes that produce this decreased lumen size may be structural, mechanical, and functional. Recent evidence that adhesion molecules like integrins and extracellular matrix components are involved in modulating the resistance vasculature in hypertension is discussed. We will not examine the important question of whether the resistance-artery phenotype is a primary abnormality or a consequence of hemodynamic or endocrine, paracrine, or autocrine trophic factors present or activated by blood pressure elevation. Whether the structural, molecular, cellular, and functional vascular changes result from a genetically programmed abnormality in some forms of hypertension has not yet been elucidated.

Structural Abnormalities of Resistance Arteries in Hypertension

Description
In hypertension, the change in structure of resistance arteries involves a combination of 2 processes, 1 termed eutrophic remodeling and the other, hypertrophic remodeling (Figure 1).5 In eutrophic remodeling, the outer diameter and the lumen are decreased and the cross-sectional area of the media is unaltered, resulting in an increased media-lumen ratio.6 This type of remodeling predominates in resistance arteries from models in which the renin-angiotensin system may be playing an important role: spontaneously hypertensive rats (SHR)7–9 and 2-kidney 1 clip Goldblatt hypertensive rats.10 In hypertensive humans, eutrophic remodeling is found in mild, essential hypertensive patients.11–14 In contrast, hypertrophic remodeling involves a thickening of the media that enroaches on the lumen. The narrowed lumen is thus associated with an increased media-lumen ratio and medial cross-
sectional area. Hypertrophic remodeling predominates in rat models of severe hypertension in which the endothelin system is activated, such as deoxycorticosterone (DOCA)-salt hypertensive rats,15 1-kidney 1 clip Goldblatt hypertensive rats,16,17 and Dahl salt-sensitive hypertension.18 In humans, it can be found in renovascular hypertension and pheochromocytoma.19 Both classes of remodeling are often present to varying degrees, and “remodeling” and “growth” indices6,20 are used to approximate the relative contribution of eutrophic and hypertrophic remodeling. One consideration that has received attention, mainly in experimental animal studies but less so in studies of human gluteal subcutaneous arteries, is the branching order of vessels. Arteries of the same branching order should be studied if comparisons between them are to be valid.

Large arterioles (lumen diameter <100 μm) likewise undergo vascular bed–specific remodeling, as reported in stroke-prone SHR.6 In smaller arterioles, an alternate abnormality may increase vascular resistance, namely rarefaction, in which temporary (functional) or permanent (anatomic) reduction of arteriolar density has been reported in several rat models of hypertension, including Dahl salt-sensitive rats,21 2-kidney 1 clip rats,22 1-kidney 1 clip hypertensive rats,23 DOCA-salt hypertensive rats,24 and SHR.25

Role of Adhesion Molecules and Extracellular Matrix

Eutrophic Remodeling

In arteries that have undergone eutrophic remodeling, the vascular wall has been restructured, so that smooth muscle cells are aligned more closely and encircle the lumen more tightly without a change in the volume of the media. Eutrophic remodeling is identified experimentally as a reduction of passive lumen and outer diameters of relaxed vessels in the absence of changes in medial cross-sectional area or vascular stiffness. Several hypotheses have been proposed to explain these changes. Maintenance of media volume may involve a combination of growth and apoptotic processes, whereby programmed cell death localized to the outer periphery of the vessel may result in a reduction of the outer diameter of the vessel, whereas inward cell growth decreases lumen diameter. Apoptosis has been reported in various models of hypertension, including aortas of DOCA-salt hypertensive rats26 and angiotensin-induced hypertensive rats.27 However, in mesenteric arteries28 and intramyocardial small arteries29 from SHR, a reduction in apoptosis has also been reported.

We have also proposed that owing to changes in extracellular matrix components and corresponding adhesion receptors, interactions between smooth muscle cells and matrix proteins shift quantitatively, topographically, or both, resulting in a rearrangement of smooth muscle cells and a restructured vascular wall (Figure 2).30 We recently reported that in SHR, the expression of adhesion molecules, specifically integrins, is abnormal. Integrins act as physical “joints” between extracellular matrix and cytoskeletal components and as signal-transducing receptors. On the basis of the

Figure 1. Schematic drawing depicting eutrophic remodeling and hypertrophic remodeling of resistance arteries in hypertension and potential agents playing roles in determining the nature of remodeling. As hypertension progresses, it is possible but unproven that eutrophic remodeling may evolve toward hypertrophic remodeling under the combined influence of angiotensin II ± endothelin-1, other growth factors, and high blood pressure. M/L indicates media-to-lumen ratio; CSA, cross-sectional area.

Figure 2. Schematic demonstration of associations between extracellular matrix (ECM) proteins and integrins on the smooth muscle cell surface and associated intracellular signaling pathways leading to cytoskeletal reorganization, cell motility, and growth. These processes contribute to rearrangement of smooth muscle cells, increased deposition of extracellular matrix components, and changes in cell-cell and cell-matrix interactions, important processes underlying mechanical alterations and structural remodeling in hypertension. G protein–coupled receptors (angiotensin, endothelin, and others) acting directly or via transactivation of growth factor receptors, as well as biomechanical strain, activate mitogen-activated protein (MAP) kinases via membrane-associated c-Src that induces association with the adaptor protein complex Shc-Grb-SOS and the downstream activation of the Ras-Raf-MAP kinase cascade. MAP kinase acts on nuclear and cytoplasmic targets to initiate cell growth. G protein–coupled receptors interact with integrins via p130cas. Extracellular matrix components directly activate integrins, and via focal adhesion kinase (FAK)–dependent pathways, phosphorylate cytoskeletal proteins (paxillin, talin, actin, etc) that regulate cytoskeletal organization and motility. Integrin-activated FAK also influences cell growth by activating MAP kinases. By mechanisms that remain unclear, integrin activation triggers opening of various channels, including L-type Ca2+ channels, modifying Ca2+ transport and vascular smooth muscle cell contraction. Functional and structural interactions between extracellular matrix proteins and smooth muscle cells through adhesion molecules may be important in maintaining vascular wall integrity. Alterations in these interactions, possibly by modifications in cell attachment sites, could contribute to changes in vascular media stiffness. FAK indicates p125 focal adhesion kinase; ERKs, extracellular signal–regulated kinases, also known as MAP kinases; and MEK, mitogen-activated ERK-activating kinase, also known as MAP kinase kinase (MAPKK). For a review, see References 100 and 110.
import of their actions, we hypothesized that vascular remodeling may involve changes in these anchorage sites. Indeed, with aging from 6 to 20 weeks, mesenteric arteries from SHR exhibited an increase in expression of α1β1 and α5β1 integrins, and in adult SHR arteries, the volume density of collagen was also markedly increased.40 Bézie et al31 also reported an increase in α1 integrins and their main ligand, fibronectin, in SHR aortas. Such changes may represent an increase in cell-matrix attachment sites and their topographic localization (clustering?) that may modulate arterial structure (Figure 2).

**Hypertrophic Remodeling**

Growth of the media of a blood vessel results in encroachment on its lumen and may involve increased smooth muscle cell number,32,33 size,16 or both (although these have not been detected consistently), as well as augmented deposition of extracellular proteins. Smooth muscle cell growth may be facilitated by several extracellular matrix proteins. One putative key player in hypertension-related vascular remodeling is tenascin-C, an extracellular matrix glycoprotein that reportedly modulates vascular smooth muscle cell proliferation. Tenascin-C colocalizes with proliferating smooth muscle cells in SHR and human hypertensive pulmonary arteries.36 Moreover, interactions between α1β1 integrins and tenasin-C promote epidermal growth factor–dependent growth and survival of rat pulmonary artery smooth muscle cells (Figure 2).37 Thus, tenascin-C or other ligands for α1β1 integrins possibly protect smooth muscle cells from apoptosis and promote proliferation. Fibronectin matrix assembly may likewise facilitate vascular smooth muscle cell growth. As mentioned previously, total fibronectin31 and α5β1 integrins30,31 are increased in arteries of SHR. This observation suggests that fibronectin matrix assembly, which requires interaction between the arginine-glycine-aspartate (RGD) site of fibronectin and α5β1 integrins,38 is also elevated in SHR vessels. Moreover, disruption of fibronectin matrix assembly inhibits vascular smooth muscle cell growth,39 underlining its potential importance in hypertrophic remodeling. Another RGD-containing protein that may be associated with proliferation is osteopontin, a secreted glycoprotein that is adhesive for vascular smooth muscle cells via αvβ3 integrins.40 In vitro studies have demonstrated that osteopontin overexpression is associated with arterial smooth muscle cell proliferation41 and may be involved in determining the synthetic/proliferative phenotype of these cells previously described in hypertension.

The synthetic phenotype of vascular smooth muscle cells that predominates in hypertension43,44 predisposes these vessels to augmented extracellular matrix deposition, a second component of hypertrophic remodeling. Increases in the volume density of collagen occur in mesenteric resistance arteries of hypertensive rats30,45 and in subcutaneous resistance arteries of patients with mild essential hypertension.46 This change may be stimulated by humoral factors whose levels or actions are enhanced in hypertension, eg, by angiotensin II.47 In the normal artery, fibrillar collagens (types I and III) are the major constituents of the intima, media, and adventitia, whereas types IV and V collagens are situated in the endothelial and smooth muscle cell basement membranes,48 along with collagen types I and III.49 Proteoglycans, nonfibrillar matrix components that carry glycosaminoglycans, are synthesized by vascular smooth muscle cells in response to growth factors.50 They may function as modulators of cell proliferation and differentiation.51 Synthesis of proteoglycans was greater in 10- and 28-week-old SHR carotid arteries52 and has also been found in smooth muscle cells from mesenteric resistance arteries in response to angiotensin II in SHR compared with Wistar rats.53 The hypertension-related accumulation of extracellular matrix proteins in resistance arteries may be facilitated by diminished matrix metalloproteinase (MMP) activity. MMPs are Zn2+- and Cu2+-dependent proteolytic enzymes that degrade extracellular matrix proteins.54-56 In the vasculature, MMPs include collagenases (eg, interstitial collagenase, or MMP-1) that digest structural or fibrillar collagens (types I through III); gelatinases (eg, gelatinases A [MMP-2] and B [MMP-9]) that digest denatured collagen (gelatin) as well as types IV and V collagen found in the subendothelial basement membrane; and stromelysins (eg, MMP-3) that digest adhesive molecules like laminin, fibronectin, nonfibrillar collagens,57 and proteoglycans.58 In sera from SHR with extensive myocardial fibrosis59,60 and in humans with essential hypertension,61 enhanced synthesis of type I collagen is not balanced by an increase in type I collagen degradation. It follows that the concentrations of MMP-1 were diminished in hypertensive patients in whom type I collagen was augmented.62 In the aortas and mesenteric arteries of stroke-prone SHR, gene expression of types I, III, and IV collagen is increased; in young SHR before hypertension was established. By resulting in collagen accumulation, this process may contribute to resistance-artery hypertrophy.63 MMP-3 activity was also decreased,64 which may promote accumulation of fibronectin and proteoglycans in SHR.51,53 Pro-MMP-2 and activated MMP-2 activities were diminished in mesenteric arteries from adult SHR,64 which could facilitate accumulation of types IV and V collagen and fibronectin.57 By modulating the extracellular matrix profile and its interactions with adhesive receptors, diminished MMP activity may contribute to remodeling of resistance arteries in hypertension.

**Mechanical Abnormalities of Resistance Arteries in Hypertension**

**Description**

The stiffness of the wall of arteries is altered in some rat models of hypertension and in essential hypertensive patients and, by influencing lumen diameter, may affect peripheral resistance to blood flow. Distensibility and compliance measure the ability of a vessel to buffer changes in pressure. Both of these measures depend on the stiffness of wall components and the geometry of the vessel and intraluminal pressure to which it is exposed. For this reason, it is important to compare vessels under isobaric conditions. Another important consideration is the level of the vasculature, branching order, or size of the vessel lumen. There may be considerable heterogeneity in distensibility with respect to vessel size. Whereas second-order cerebral small arteries from stroke-prone SHR exhibit...
decreased distensibility, accounting for their apparent reduction in external diameter, third-order small arteries of <200 μm exhibit remodeling with normal wall mechanics.65 There may be other examples of this type of heterogeneity. The slope of incremental elastic modulus plotted versus vascular wall stress is a geometry-independent measure of the stiffness of wall components, which include connective tissue, smooth muscle cells, endothelial cells, and more important, collagen and elastin (less and more distensible components, respectively). In genetic and experimental rat models of salt-sensitive hypertension such as Dahl salt-sensitive rats66 and DOCA-salt rats,67 respectively, mesenteric resistance-artery stiffness was normal compared with that in normotensive controls. However, in SHR the stiffness of mesenteric small arteries may be reduced initially.68 This feature is followed by increases in the stiffness of wall components, with reduced compliance and distensibility in association with increased collagen deposition.69 In 2-kidney 1 clip renal hypertensive rats 1 and 5 weeks after renal artery clipping, carotid arteries had normal mechanics under isobaric conditions, whereas after 9 and 24 weeks, they had become stiffer.69 As already mentioned, second-order cerebral small arteries from stroke-prone SHR exhibit increased stiffness, whereas smaller third-order arteries in the same vascular bed have decreased stiffness.65 In humans, progressive arterial stiffening and decreased vascular compliance under isobaric conditions occur as individuals age or develop hypertension.70 However, independent of the presence of arterial hypertrophy, increased elasticity has been shown in the aorta71 but not in the radial artery.72 Elastic modulus was not increased in subcutaneous small arteries from hypertensive patients when these vessels were studied by the wire-myograph technique.73 We have found slightly decreased stiffness of wall components in resistance arteries obtained from mildly hypertensive patients that were studied isobarically.46 Subsequently, we found in other groups of subjects no difference in the incremental elastic modulus versus stress of subcutaneous resistance arteries between normotensive subjects and age-matched hypertensive patients,74 consistent with the results of Thybo et al.73 In the remodeled small artery in hypertension, with more closely aligned cellular and fibrillar components due to changes in adhesion of cellular and fibrillar structures, early in the disease collagen fibrils may be recruited at higher distending pressures in small arteries from mildly hypertensive patients than in vessels from normotensives, whereas later, compliance of resistance arteries in hypertensives may be reduced, in part owing to the smaller lumen, greater collagen-elastin ratio, and the engagement of collagen fibers and resulting tensing of the collagen jacket at earlier portions of the pressure curve. The potential influence of perivascular collagen on vascular stiffness has not been evaluated.

**Role of Adhesion Molecules and Extracellular Matrix**

The earliest reports of changes in the mechanics of resistance arteries that were not the expected increased stiffness were the observations of decreased wall stiffness in cerebral arterioles from stroke-prone SHR,65,75 an abnormality attributed to increased elastin content.76 In contrast, in peripheral resistance arteries, namely mesenteric, vessel wall stiffness was increased in SHR79 and was associated with an increased volume density of collagen, an increased collagen-elastin ratio, or both.30,42 An important but confounding finding was that vascular stiffness was decreased in subcutaneous resistance arteries from patients with mild essential hypertension, despite an increased collagen-elastin ratio.46 Although collagen is increased in hypertensive resistance arteries, the subtypes of collagen present in the vascular wall may be important determinants of stiffness. Conduit-artery stiffness in genetically hypertensive rats is influenced not only by hypertension per se but also by differences in the contents of collagen subtypes.77 Aortas of 6- and 20-week-old SHR were stiffer than in age-matched Wistar-Kyoto rats, in association with a 2-fold increase of type V collagen,78 fibronectin, or both,31 consistent with the finding that MMP-2, which degrades primarily types IV and V collagen and fibronectin,57 and MMP-3 activity are diminished in adult SHR mesenteric arteries.64 Fibronectin gene expression was not increased.31 Extracellular constituents other than collagen and elastin, such as proteoglycans, may modulate vascular stiffness. These molecules are nonfibrillar matrix components present in resistance artery smooth muscle cells from SHR90 and are enhanced in their carotid arteries.53 Removal of 65% of chondroitin-dermatan sulfate–containing glycosaminoglycans from mesenteric resistance arteries increased their stiffness.79 In human resistance arteries from mild essential hypertensives, in whom vascular stiffness is initially paradoxically decreased despite increased collagen-elastin ratios,46 there may be an increase in proteoglycans. Finally, abnormal interactions between extracellular matrix proteins, smooth muscle cells, and adhesion receptors may be the most important element by which stiffness is modulated via changes in cell attachment to fibrillar components of the extracellular matrix.

**Functional Abnormalities of Resistance Arteries in Hypertension**

**Description**

Abnormal resistance-artery function in hypertension may increase peripheral resistance by reducing lumen diameter, owing to enhanced constriction. Early in experimental hypertension, increased responsiveness to norepinephrine and enhanced myogenic tone have been reported.80–82 Impaired endothelium-dependent relaxation may also contribute, and indeed, reductions in acetylcholine-induced and flow-mediated vasodilatation in rat and human resistance arteries have been extensively documented.83–85 Enhanced vasoconstriction is often cited as a mechanism for increased vascular tone in hypertension and has been reported in human vessels80 and in experimental hypertension.86 However, for the most part, hormones such as endothelin-1 and vasopressin as well as norepinephrine elicit normal or diminished constrictor responses,87–89 suggesting that augmented vasoconstriction in hypertension may largely be due to the amplifying effect of structural or mechanical reduction of lumen diameter, according to the law of Laplace.90,91 There is nonetheless evidence
that argues against this hypothesis. This has triggered a spirited debate between groups of investigators who do not believe that structurally based enhancement of vasoconstriction occurs in hypertension and those who do. Augmented vasconstriction has also been reported in response to angiotensin II, the mechanism of which is not completely understood. This may be due to postreceptor signaling changes, either in the coupling of the receptor by G proteins or other events in the signaling cascade, leading to enhanced calcium release and entry into the smooth muscle cells that have been reported in vascular smooth muscle in experimental and human hypertension.

Role of Adhesion Molecules and Extracellular Matrix

Extracellular matrix components may also contribute to abnormal function of resistance arteries in hypertension (Figure 2). Peptides carrying the minimal integrin-binding sequence RGD have induced rapid, endothelium-dependent and slower, endothelium-independent relaxation of rat aortic rings. Synthetic RGD peptides or proteolized RGD-containing fragments of collagen I have induced relaxation of rat skeletal muscle arterioles via binding to \( \alpha_\beta \) integrins. Ligand binding to \( \alpha_\beta \) integrins with RGD peptides, vitronectin, or fibronectin may relax vessels by reducing intracellular calcium levels in vascular smooth muscle cells, possibly by modifying activation of K channels and L-type Ca\(^{2+} \)-channels (Figure 2). Because \( \alpha_\beta \) integrins are more abundant in arteries from adult SHR, \( \alpha_\beta \)-mediated relaxation should be enhanced. However, in hypertension, \( \alpha_\beta \) integrins may be occupied, unavailable for ligand binding, and therefore unable to mediate a relaxatory effect.

RGD peptides also interact with integrins to cause vascular constriction. In rat skeletal muscle arterioles, selective stimulation of abluminal but not luminal \( \alpha_\beta \) integrins with GRGDNP (where N indicates asparagine and P, proline) have produced arteriolar constriction that was endothelium dependent and mediated by endothelin. Afferent arteriolar constriction occurred in response to GRGDSP (where S indicates serine) in the presence of \( N^\delta \)-nitro-L-arginine methyl ester, with a concomitant increase in intracellular calcium concentration. Binding to \( \alpha_\beta \) integrins increased L-type Ca\(^{2+} \) currents in skeletal arteriolar smooth muscle cells. In cultured pulmonary vascular smooth muscle cells in which changes in cytoskeletal stiffness paralleled cell contraction and relaxation in response to endothelin-1, cytoskeletal contractile tone increased in direct proportion to the increasing density of fibronectin coating. This finding suggests that in hypertensive arteries, where fibronectin and, with age, \( \alpha_\beta \) integrins are increased, \( \alpha_\beta \) integrin occupancy may contribute to increased contractility and vascular resistance. Other extracellular matrix molecules may influence vascular function. Inhibition of vascular MMP-2 in rat mesenteric arteries reduced the vasoconstrictor effects of big endothelin-1. MMP-2 cleaves big endothelin-1 to release endothelin-1, a new vasoconstrictor peptide.

Conclusions

Abnormalities of endothelial or smooth muscle cells, adhesion molecules, and extracellular matrix in the vasculature may contribute to structural, mechanical, or functional changes that reduce the lumen size of small arteries and arterioles, thereby increasing vascular resistance in hypertension. Understanding these vascular alterations and the mechanisms whereby they are generated may offer important insights that may help in the development of therapies contributing to the prevention of vasculature-initiated end-organ damage in cardiovascular disease.

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