Vascular Remodeling in Hypertension
Roles of Apoptosis, Inflammation, and Fibrosis

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Abstract—Remodeling of large and small arteries contributes to the development and complications of hypertension. The focus of this review is some of the mechanisms involved in the remodeling of small arteries in hypertension. In hypertension, changes in small artery structure are basically of 2 kinds: (1) inward eutrophic remodeling, in which outer and lumen diameters are decreased, media/lumen ratio is increased, and cross-sectional area of the media is unaltered; and (2) hypertrophic remodeling, in which the media thickens to encroach on the lumen, resulting in increased media cross-sectional area and media/lumen ratio. Growth, apoptosis, inflammation, and fibrosis contribute to vascular remodeling in hypertension. Apoptosis is gene-regulated cell death, with minimal membrane disruption and inflammation, that counters cell proliferation and fine-tunes developmental growth. Apoptosis has been reported in hypertension to be both increased and decreased in different tissues, including blood vessels. Inflammation, which may be low grade, probably plays an important role in triggering fibrosis in cardiovascular disease and hypertension. Vascular fibrosis entails accumulation of collagen, fibronectin, and other extracellular matrix components in the vessel wall and is an important aspect of extracellular matrix remodeling in hypertension. Associated with this, there may be increases in cell-matrix attachment sites (integrins) and changes in their topographical localization that may modulate arterial structure. Imbalance in matrix metalloproteinase/tissue inhibitors of metalloproteinases may contribute to alteration in collagen turnover and extracellular matrix remodeling. Chronic vasoconstriction may lead to embedding of the contracted vessel structure in a remodeled extracellular matrix, contributing to the inward remodeling of the blood vessel as smooth muscle cells are rearranged around a smaller lumen. The resulting remodeling of small arteries may initially be adaptive, but eventually it becomes maladaptive and compromises organ function, contributing to cardiovascular complications of hypertension. (Hypertension. 2001;38[part 2]:581-587.)

Key Words: arteries ■ apoptosis ■ inflammation ■ fibrosis ■ collagen ■ muscle, smooth

In hypertension, resistance arteries undergo eutrophic and/or hypertrophic remodeling. In inward eutrophic remodeling, outer and lumen diameters are reduced, media cross-sectional area is unaltered, and media/lumen ratio is increased, without stiffening. Spontaneously hypertensive (SHR) and 2-kidney, 1-clip Goldblatt rats, as well as mild essential hypertensive patients, exhibit predominantly inward eutrophic remodeling. When media growth encroaches on the lumen to increase the media/lumen ratio, the change has been called hypertrophic remodeling. It predominates in severe hypertension, such as in deoxycorticosterone acetate (DOCA)-salt rats, 1-kidney, 1-clip (1K1C) Goldblatt rats, Dahl salt-sensitive rats, and humans with secondary hypertension. Growth, apoptosis, inflammation, and fibrosis are all mechanisms that have been invoked to contribute to arterial remodeling in hypertension. Increased growth has been classically implicated in arterial remodeling in hypertension. Chronic vasoconstriction associated with mild inflammation and activation of deposition of collagen, fibronectin, and other components of the extracellular matrix may result in a remodeled arterial structure with a smaller lumen and increased media/lumen ratio, ie, the inward eutrophic remodeled vessel. This review will center on events taking place in the media of the vessel wall during vascular remodeling. Although the endothelium may participate in some of these effects to an important degree, its contribution will only be addressed peripherally, and the reader is directed to the many reviews on the subject.

Apoptosis

The finding that inward eutrophic remodeling may be predominant in some forms of hypertension has raised the possibility that growth may be compensated or modified by countervailing mechanisms in hypertension, particularly apoptosis. Apoptosis is gene-regulated cell death, first recognized in development as a mechanism involved in the fine-tuning of growth. Apoptosis is also invoked in cancer, immune diseases, Parkinson’s disease, and Alzheimer’s de-
mentia and has been reported to different degrees in atherosclerosis, restenosis, myocardial infarction, and heart failure. Apoptosis is increased in hypertensive rat heart, brain, kidney, and arteries, where smooth muscle cell (SMC) death modulates remodeling. Aorta of DOCA-salt rats displays increased apoptosis, as shown by DNA laddering, augmented in situ end-labeling of fragmented DNA, and/or Bax/Bcl-2 ratio. Vascular SMCs in hypertensive rats are more prone to apoptosis, suggesting that in these beds, apoptosis influences vascular resistance via rarefaction, as in 1KIC Goldblatt hypertensive rats.

The role of apoptosis in vascular remodeling remains unclear. In inward eutrophic remodeling, a combination of growth and apoptosis, with apoptosis localized to the outer periphery, reduces the outer diameter of the vessel, whereas inward growth decreases lumen diameter, which may explain the maintenance of media volume. Whether apoptosis is a growth-related compensatory mechanism or a primary process remains to be clarified. Interestingly, there are reports of reduced SMC apoptosis in the small arteries of young SHR, suggesting that a decrease in the apoptotic rate in resistance blood vessels contributes to their enhanced growth in this model. Apoptosis modulators in the vasculature are numerous and complex. Candidates may include reactive oxygen species, NO, angiotensin type 2 (AT 2 ) receptors, and the endothelin system. Reactive oxygen species are involved in the pathogenesis of hypertension and in apoptosis of vascular cells, where, specifically, O 2 − induces proliferation and H 2 O 2 may induce apoptosis via a protein kinase C–dependent mechanism. Angiotensin (Ang) II is also a potential trigger of apoptosis. Ang II infusion in normotensive rats raised blood pressure and increased apoptotic rate in thoracic aorta by activation of angiotensin type 1 (AT 1 ) and AT 2 receptor subtypes. Indeed, following AT 1 receptor blockade in SHR, vascular SMC apoptosis increased, an effect attenuated by AT 1 receptor antagonism. In rat aortic SMC, cyclic stretch increased endothelin B (ET B ) receptor mRNA and promoted ligand occupancy of the resultant receptors by reducing endothelin A (ET A ) receptor mRNA. Exogenous endothelin induced apoptosis via ET A receptors. On the other hand, there is evidence for a survival and anti-apoptotic effect mediated by endothelin A (ET A ) receptors.

Apoptosis, Vascular Remodeling, and Results of Therapy

Vascular remodeling contributes to end-organ damage in hypertension, providing a rationale for regression of remodeling of blood vessels as a therapeutic aim. Large conductance Ca 2+ channel blockers stimulate SMC apoptosis, as shown by studies with nifedipine and amlodipine on SHR thoracic aorta SMCs and with verapamil on rat coronary artery SMCs. During early treatment, ACE inhibition, AT 1 receptor antagonism, and Ca 2+ channel blockade stimulated medial SMC apoptosis in thoracic aorta of SHR, although mere blood pressure lowering by hydralazine had no effect. Some studies suggested that apoptosis occurs in waves for limited periods. In other studies, increased apoptotic rate persisted through 12 weeks of treatment with enalapril and amlodipine and through 16 weeks with quinapril. Increased apoptosis also occurs in aortae of DOCA-salt rats, and treatment with ET A-selective endothelin receptor antagonists enhances apoptosis in this model. Antihypertensive therapy may therefore contribute to regression of vascular wall growth via activation of pro-apoptotic mechanisms.

Inflammation

The actions of Ang II are mediated in large measure by stimulation of production of superoxide anion and activation of redox-sensitive genes. Some of these include genes participating in inflammatory responses to angiotensin stimulation. Among these are nuclear factor κB and AP-1, associated with upregulation of adhesion molecules such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, and stimulation of the production of chemokines such as monocyte chemotactic protein 1 followed by recruitment of monocytes/macrophages to the vascular wall. In rats doubly transgenic for human renin and human angiotensinogen, which develop a malignant form of hypertension, inflammatory mediators were shown to be activated, with upregulation of adhesion molecules in the kidney and infiltration by monocyte-macrophages. Although the latter processes and the role of Ang II in triggering them have been clearly identified in the heart and kidney and play a role in the progression of atherosclerosis in large conduit vessels, their participation in small artery remodeling is only now starting to be investigated. We have often noted that in small arteries, increased numbers of inflammatory cells may be observed in hypertension in the adventitia, an often neglected layer of the vascular wall. Indeed, the adventitia has recently been identified as an important source of oxygen free radicals potentially participating in vascular pathophysiology. It is likely that inflammation and the increased oxidative stress, which probably act as an important trigger and may to a large extent be Ang II–dependent, play a role in the process leading to remodeling of small and large vessels in hypertension. Nonetheless, this remains to be further investigated. As well, the potential importance of inflammation in the vascular wall from a therapeutic viewpoint remains an interesting but largely unexplored area of potential application of the new knowledge of participation of inflammatory mediators in remodeling of the vasculature.

Vascular Fibrosis

Fibrillar extracellular matrix in the vessel wall includes structural proteins (collagen and elastin) and adhesive proteins (eg, laminin and fibronectin). In hypertension, vascular fibrosis entails in large part, the deposition of extracellular matrix, particularly collagen, in the arterial wall. In normal arteries, fibrillar collagens I and III are major constituents of the intima, media, and adventitia, whereas types I, III, IV, and...
V are in endothelial and SMC basement membranes.\textsuperscript{58} There are early reports\textsuperscript{47-48} of increased collagen synthesis in the arterial wall in hypertension that occurred globally in SHR and DOCA-salt rat aortae, mesenteric arteries, cerebral microvessels, pial arteries, and basilar arteries. Collagen accumulation may not follow synthesis and may be bed specific, as it occurs in coronary arteries\textsuperscript{49} but less consistently in aortae of SHR\textsuperscript{50} or DOCA-salt rats,\textsuperscript{51} although recent studies report increases in collagen III but not collagen I in Japanese and Lyon SHR strains.\textsuperscript{52} In SHR-sp aortae, total collagen is not augmented.\textsuperscript{53} Nonetheless, upregulated gene expression of types I, III, and IV was detected in aortae and mesenteric arteries.\textsuperscript{54} Collagen was reported increased in mesenteric small arteries of SHR\textsuperscript{55,56} or subcutaneous resistance arteries from essential hypertensive humans.\textsuperscript{57} Collagen is the extracellular fibrillar component that may alter the passive pressure/diameter relation of arteries at higher pressures and induce a progressive stiffening of the vascular wall. However, we showed in small arteries from these relatively young humans with mild to moderate hypertension that increased collagen deposition may be associated with reduced stiffness.\textsuperscript{57} This indicates that it is not the amount of collagen in the wall but rather the recruitment of collagen fibers at higher pressures that results in increased stiffness of the vessel wall. Early in hypertension, both in experimental animals and in humans, the vessel wall components may be less stiff in spite of increased collagen deposition, but as hypertension progresses, other changes, particularly in extracellular matrix–SMC anchoring, may result in normalization of wall stiffness.\textsuperscript{58} Later, the increased stiffness that occurs in advanced hypertension may develop.\textsuperscript{59} Fibronectin also accumulated in DOCA-salt,\textsuperscript{60} SHR,\textsuperscript{61} Dahl salt-sensitive,\textsuperscript{62} SHR-sp,\textsuperscript{63} and Ang II–infused rat aortae,\textsuperscript{64} probably independently of blood pressure. In many of these models, stimulation of AT\textsubscript{1} receptors is the likely mechanism. However, the extent to which fibronectin accumulates in resistance arteries in hypertension is presently unclear, although we have preliminary evidence (Q. Pu and E.L. Schiffrin, unpublished, 2001) using confocal microscopy that demonstrated increased fibronectin in the media of resistance arteries of SHR-sp.

Ang II stimulates human vascular SMC production of collagen I,\textsuperscript{65} activating the procollagen type I gene via the mitogen-activated protein kinase/ERK pathway.\textsuperscript{66} These effects are mediated, at least in part, by AT\textsubscript{1} receptors.\textsuperscript{62,64,65} AT\textsubscript{2} receptors may also play a role\textsuperscript{67,68} via G\textsubscript{0} proteins.\textsuperscript{69} Involvement of angiotensin evokes the possible involvement of multiple autocrine growth factors that modulate the responses to angiotensin, such as transforming growth factor–\beta (TGF-\beta) and platelet-derived growth factor,\textsuperscript{70} as well as other growth factors, including insulin-like growth factor and basic fibroblast growth factor. Ang II increased TGF-\beta in a losartan-sensitive manner, and in human arterial SMC, angiotensin-stimulated collagen synthesis was inhibited by blocking TGF-\beta.\textsuperscript{71} A relationship between Ang II and TGF-\beta was suggested previously, in which stretch was the experimental stimulus of collagen synthesis in rabbit aortic SMC.\textsuperscript{72} Stretch concomitantly increased immunoreactive Ang II and TGF-\beta in the culture medium, and elicited collagen synthesis. Angiotensin antagonism attenuated TGF-\beta secretion and collagen synthesis. Collagen synthesis was inhibited by TGF-\beta neutralizing antibody or truncated TGF-\beta type II receptor, suggesting a linear pathway where Ang stimulates TGF-\beta secretion, which in turn triggers collagen synthesis. Indeed, exogenous TGF-\beta in aortic SMC results in collagen synthesis,\textsuperscript{72} and in human cells, role of TGF-\beta in stretch-induced collagen synthesis was also detected.\textsuperscript{73} However, in SHR SMC these effects of TGF-\beta were blunted versus WKY.\textsuperscript{74}

Other modulators of collagen synthesis include aldosterone and endothelin. Aortic collagen accumulation was attenuated by inhibiting ACE\textsuperscript{21} or by antagonizing aldosterone.\textsuperscript{75} Collagen I synthesis is stimulated by endothelin-1 (ET-1) in coronary artery SMC.\textsuperscript{76} Indeed, in the N\textsubscript{ω}-nitro-L-arginine methyl ester (L-NNAME) model of hypertension, ET-1 synthesis is increased in renal microvessels and activates local collagen formation.\textsuperscript{77} Losartan blocked L-NNAME–induced fibrosis, and stimulatory effects of angiotensin on collagen I to III chain promoter activity were attenuated by endothelin receptor antagonism.\textsuperscript{78} In DOCA-salt hypertensive rats, which have very significant cardiac fibrosis, administration of an ET\textsubscript{A} receptor antagonist ameliorated interstitial and perivascular fibrosis.\textsuperscript{79} In aldosterone-infused rats, vascular changes were prevented by endothelin antagonism,\textsuperscript{80} and collagen deposition in heart and arteries was also demonstrated to be endothelin dependent.\textsuperscript{81} Cardiovascular fibrosis is, in large part, a humoral-determined event, with central roles of Ang II, ET-1, and mineralocorticoids.

Matrix metalloproteinase (MMP) activity may modulate hypertension-related accumulation of extracellular matrix proteins in resistance arteries. MMPs are Zn\textsuperscript{2+}– and Ca\textsuperscript{2+}-dependent proteolytic enzymes that degrade extracellular matrix proteins.\textsuperscript{82,83} Several different MMPs are present in the vasculature. These include collagenses (e.g., interstitial collagenase MMP-1 and MMP-13) that digest structural or fibrillar collagens (types I to III). Gelatinases A (MMP-2) and B (MMP-9), which digest denatured collagen (gelatin) and collagen types IV and V, are found in the subendothelial basement membrane. Stromelysins (e.g., MMP-3) are also found. They digest adhesive molecules such as laminin, fibronectin, nonfibrillar collagens, and proteoglycans. Finally, there are the membrane-type MMPs (MT1-MMP or MMP-14). MT1-MMP activates other MMPs,\textsuperscript{84} MT1-MMP and MMP-2 act as an integral part of multiprotein enzymatic complex. MT1-MMP may activate latent MMP-13, which in turn activates MMP-9. MT1-MMP may form a ternary complex with tissue inhibitors of metalloproteinase (TIMP)-2 and pro-MMP-2 that depends on the tethering of pro-MMP-2 by \( \alpha_\text{v}\beta_5\)-integrin. Indeed, a number of integrins, including \( \alpha_\text{qin}\), may be involved in activation of MMPs. MMP-mediated modulation of extracellular matrix could result via integrin-mediated signaling in cytoskeletal reorganization. This could contribute to both differential restructuring of extracellular matrix proteins and reorganization of SMCs in the vascular wall in hypertension. In serum from SHR with extensive myocardial fibrosis\textsuperscript{85,86} and in humans with essential hypertension,\textsuperscript{87} markers of enhanced synthesis of type I collagen are not balanced by markers of increased type I collagen degradation. In hypertensive patients in whom type I collagen precursors were augmented, serum concentrations of MMP-1 were in fact reduced.\textsuperscript{88} MMP-1 activity
was decreased in the mesenteric arterial bed of young SHR before hypertension was established.89 MMP-3 activity was also decreased, which may promote accumulation of fibronectin and proteoglycans in SHR.90,91 Pro-MMP2 and activated MMP-2 activities were diminished in mesenteric arteries from adult SHR,89 which could facilitate accumulation of types IV and V collagen and fibronectin.94 Changes in MMP activity may thus contribute to resistance artery remodeling in hypertension by modulating extracellular matrix profile and interacting with adhesion receptors. Significant decreases in MMP activity in young SHR-sp vessels could result in decreased collagen turnover and increased collagen accumulation, whereas in the older hypertensive rats, vascular increased MMP activity suggests countervailing activation of MMPs or inhibition of activity of TIMPs to reduce collagen accumulation in the vascular wall.

We have proposed that remodeling of the small arteries occurring in both humans and experimental models of hypertension implies a remodeling of the extracellular matrix and of extracellular–vascular SMC attachment sites and a restructuring of vascular SMCs that may in part be triggered by the adhesion molecules that mediate anchoring to ECM components. These adhesion molecules (integrins) transduce signals from the extracellular to the cytoskeletal fibrillar components.27 Because of changes in extracellular matrix components and corresponding adhesion receptors, interactions between SMCs and matrix proteins shift, quantitatively and/or topographically, resulting in a rearrangement of SMCs and a restructured vascular wall. We hypothesized that vascular remodeling may involve changes in these attachment sites. We have shown that expression of integrins is abnormal in SHR blood vessels and is modulated by age.55 Mesenteric arteries from SHR exhibited an increase in expression of αβ3- and αβ1-integrins from 6 to 20 weeks. In arteries from adult SHR, the volume density of collagen was significantly increased.55 Bézie et al50 have also reported increases in α1-integrins and fibronectin, their main ligand, in aorta from SHR. Such changes may represent an increase in cell–extracellular matrix attachment sites and perhaps also their topographical localization that may modulate arterial structure. One may envision that in the hypertensive state, progressive deposition of extracellular matrix fibrillar components anchored to SMCs of the chronically constricted vessel may result in an artery with a persistently smaller lumen, as found in the inward eutrophic remodeling characteristic of small arteries of SHR and in essential hypertension. In addition, changes in the attachment of the fibrillar elements of the matrix may occur that contribute to arterial inward remodeling by altering the anchoring of SMC to fibrillar components of the extracellular matrix. This would also alter signal transduction by integrins from outside the cell to the SMC cytoskeleton, promoting restructuring of the SMC in the vessel wall.

Growth of the smooth muscle in the media of blood vessels may be facilitated by several extracellular matrix proteins. Tenascin-C, an extracellular matrix glycoprotein and ligand for αβ1, is one such extracellular component that may be important in vascular remodeling in hypertension. It co-localizes with proliferating SMCs in SHR82 and may be a survival factor that promotes proliferation and protects SMCs from apoptosis. Fibronectin matrix assembly may likewise facilitate vascular SMC growth. As mentioned previously, total fibronectin80 and αβ1-integrins80,55 are increased in arteries of SHR. This suggests that fibronectin matrix assembly, which requires the interaction between the arginine-glycine-aspartate site of fibronectin and αβ3-integrins,93 is also elevated in SHR vessels. Another arginine-glycine-aspartate–containing protein that may be associated with proliferation is osteopontin, a secreted glycoprotein adhesive for vascular SMCs via αβ3-integrins.94 In vitro studies have demonstrated that osteopontin overexpression is associated with arterial SMC proliferation.95

**Fibrosis, Vascular Remodeling, and Therapy**

Arterial wall thickening may increase peripheral resistance and blood pressure, in part by physically encroaching on the lumen and, where collagen is invoked, by increasing wall stiffness to reduce lumen diameter at a given pressure.27 In SHR resistance arteries, collagen density or relative content was normalized by ACE inhibition,55,56 AT1 receptor blockade,55 and the dihydropyridine Ca2+-channel blocker amlo-dipine.56 Aldosterone antagonism also reduced collagen in SHR aortae.96 Likewise, in vessels from SHR-sp and DOCA-salt rats, AT1 receptor antagonist reduced collagen types I, III, and IV mRNA.63 At least in SHR, amelioration of collagen accumulation is not due to blood pressure lowering per se, as minoxidil had no effect on collagen content in aortae or in renal and superior mesenteric arteries.96 Thus, regression of vascular fibrosis may occur independently of blood pressure lowering.

**Conclusion**

In hypertension, vascular remodeling contributes to increased peripheral resistance, impacting both development and complications of hypertension. Although growth is the mechanism that is more classically associated with vascular remodeling, it has increasingly been appreciated that apoptosis, low-grade inflammation, and vascular fibrosis are dynamic processes that also may influence the degree of remodeling that occurs (summarized in the Figure). Inward growth may be associated with peripheral apoptosis, contributing to eutrophic remodeling. Low-grade inflammation, perhaps angiotensin- or endothelin-dependent and triggered in part by increased oxidative stress in the vascular wall stimulated by these peptides or other agents, may elicit growth factor–mediated extracellular matrix remodeling. Changes in the anchoring of cells to extracellular fibrillar components may alter cell attachment, changing the architecture of the vessel wall, and may promote abnormal intracellular transduction of extracellular input to the cytoskeleton of SMC, contributing to SMC cell restructuring. Chronic vasoconstriction may result in an inwardly remodeled blood vessel as the contracted vessel structure becomes embedded in a remodeled extracellular matrix, further promoting re-arrangement of SMCs around a smaller lumen. Growth, apoptosis, inflammation, and fibrosis of blood vessels may thus all contribute to vascular remodeling. The resulting arterial remodeling may initially be adaptive but eventually becomes maladaptive and compromises organ function, contributing to cardiovascular
Proposed model of the pathophysiologic mechanisms leading to small artery remodeling in hypertension. Blood pressure (BP) may rise progressively as a result of genetically and/or environmentally determined increased neurohumoral/hormonal (endocrine, paracrine, or autocrine) drive. Either directly or indirectly via the action of vasoactive peptides such as Ang II and ET-1, mediated in part by increased oxidative stress, vasoconstriction is induced and SMC growth and apoptosis, low-grade inflammation, and vascular fibrosis occur, leading to vascular remodeling. Vascular remodeling may feed back by amplifying BP elevation. SMC growth and apoptosis, low-grade inflammation, and vascular fibrosis are dynamic processes that influence vessel remodeling. Inward growth associated with peripheral apoptosis may lead to eutrophic remodeling. Low-grade inflammation, perhaps triggered by Ang II or ET-1 stimulation of oxidative stress in the vascular wall, may promote growth factor–mediated extracellular matrix remodeling. Changes in the anchoring of cells to extracellular fibrillar components may alter extracellular-SMC attachments (integrins), changing the architecture of the vessel wall, and the intracellular transduction of extracellular signals to the SMC cytoskeleton, favoring restructuring of SMC cells. Changes in MMP/TIMPs may contribute to alteration in collagen turnover and promote extracellular matrix remodeling. Chronic vasoconstriction may lead to embedding of the contracted vessel structure in a remodeled extracellular matrix, contributing to the inward remodeling of the blood vessel as SMCs become rearranged around a smaller lumen. Growth, apoptosis, inflammation, and fibrosis in the blood vessel wall may thus all contribute to vascular remodeling. Although not developed in the text, endothelial dysfunction, in part induced by BP elevation and mediated by reduced NO bioavailability as NO is scavenged by oxygen free radicals, also participates in vascular remodeling. NO would under normal conditions inhibit vasoconstriction, growth, and collagen deposition and promote apoptosis. Remodeling may initially be adaptive but eventually becomes maladaptive and compromises organ function, contributing to cardiovascular complications of hypertension.

complications of hypertension. Accordingly, growth, apoptosis, inflammation, and fibrosis all are important end points and attractive therapeutic objectives in hypertensive vascular disease.

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