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

Hope D. Intengan, Ernesto L. Schiffrin

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.1 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)1-2 and 2-kidney, 1-clip Goldblatt1 rats, as well as mild essential hypertensive patients,3,4 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,5 1-kidney, 1-clip (1K1C) Goldblatt rats,6-8 Dahl salt-sensitive rats,9 and humans with secondary hypertension.10 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.11 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.12 Apoptosis is also involved in cancer, immune diseases, Parkinson’s disease, and Alzheimer’s de-
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\(^{35}\) and amlodipine\(^{21}\) on SHR thoracic aorta SMCs and with verapamil on rat coronary artery SMCs.\(^{36}\) 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.\(^{37}\) Some studies suggested that apoptosis occurs in waves for limited periods.\(^{19,34,37}\) In other studies, increased apoptotic rate persisted through 12 weeks of treatment with enalapril andamlodipine\(^{21}\) and through 16 weeks with quinapril.\(^{38}\) Increased apoptosis also occurs in aortae of DOCA-salt rats, and treatment with ET\(_A\)-selective endothelin receptor antagonists enhances apoptosis in this model.\(^{19}\) 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.\(^{39}\) Some of these include genes participating in inflammatory responses to angiotensin stimulation.\(^{40–42}\) Among these are nuclear factor \(\kappa\)B 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.\(^{43}\) Although the latter processes and the role of Ang II in triggering them have been clearly identified in the heart and kidney\(^{43}\) 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. However, 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.\(^{45}\) 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.\(^{46}\) 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. There are early reports 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 but less consistently in aortae of SHR or DOCA-salt rats, although recent studies report increases in collagen III but not collagen I in Japanese and Lyon SHR strains. In SHR-sp aortae, total collagen is not augmented. Nonetheless, upregulated gene expression of types I, III, and IV was detected in aortae and mesenteric arteries. Collagen was reported increased in mesenteric small arteries of SHR or subcutaneous resistance arteries from essential hypertensive humans. 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. 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 anchoring, may result in normalization of wall stiffness. Later, the increased stiffness that occurs in advanced hypertension may develop. Fibronectin also accumulated in DOCA-salt, SHR, Dahl salt-sensitive, SHR-sp, and Ang II-infused rat aortae, probably independently of blood pressure. In many of these models, stimulation of AT_2 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, activating the procollagen type I gene via the mitogen-activated protein kinase/ERK pathway. These effects are mediated, at least in part, by AT_1 receptors. AT_2 receptors may also play a role via Gα_

Involvement of angiotensin evokes the possible involvement of multiple autocrine growth factors that modulate the responses to angiotensin, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor, as well as other growth factors, including insulin-like growth factor and basic fibroblast growth factor. Ang II increased TGF-β in a losartan-sensitive manner, and in human arterial SMC, angiotensin-stimulated collagen synthesis was inhibited by blocking TGF-β. A relationship between Ang II and TGF-β was suggested previously, in which stretch was the experimental stimulus of collagen synthesis in rabbit aortic SMC. Stretch concomitantly increased immunoreactive Ang II and TGF-β in the culture medium, and elicited collagen synthesis. Angiotensin antagonism attenuated TGF-β secretion and collagen synthesis. Collagen synthesis was inhibited by TGF-β neutralizing antibody or truncated TGF-β type II receptor, suggesting a linear pathway where Ang stimulates TGF-β secretion, which in turn triggers collagen synthesis. Indeed, exogenous TGF-β in aortic SMC results in collagen synthesis, and in human cells, a role of TGF-β in stretch-induced collagen synthesis was also detected. However, in SHR SMC these effects of TGF-β were blunted versus WKY.

Other modulators of collagen synthesis include aldosterone and endothelin. Aldosterone accumulation was attenuated by inhibiting ACE or by antagonizing aldosterone. Collagen I synthesis is stimulated by endothelin-1 (ET-1) in coronary artery SMC. Indeed, in the Nω-nitro-l-arginine methyl ester (L-NAME) model of hypertension, ET-1 synthesis is increased in renal microvessels and activates local collagen formation. Losartan blocked L-NAME–induced fibrosis, and stimulatory effects of angiotensin on collagen I-α2 chain promoter activity were attenuated by endothelin receptor antagonism. In DOCA-salt hypertensive rats, which have very significant cardiac fibrosis, administration of an ETα receptor antagonist ameliorated interstitial and perivascular fibrosis. In aldosterone-infused rats, vascular changes were prevented by endothelin antagonism, and collagen deposition in heart and arteries was also demonstrated to be endothelin dependent. 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 Zn2+- and Ca2+-dependent proteolytic enzymes that degrade extracellular matrix proteins. Several different MMPs are present in the vasculature. These include collagenases (eg, 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 (eg, 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, and MMP-1 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 α5β1 integrin. Indeed, a number of integrins, including α5β1, 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 and in humans with essential hypertension, 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. MMP-1 activity...
was decreased in the mesenteric arterial bed of young SHR before hypertension was established.\textsuperscript{89} MMP-3 activity was also decreased, which may promote accumulation of fibronectin and proteoglycans in SHR.\textsuperscript{90,91} Pro-MMP2 and activated MMP-2 activities were diminished in mesenteric arteries from adult SHR,\textsuperscript{89} which could facilitate accumulation of types IV and V collagen and fibronectin.\textsuperscript{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.\textsuperscript{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.\textsuperscript{55} Mesenteric arteries from SHR exhibited an increase in expression of \(\alpha_v\beta_3\) and \(\alpha_v\beta_5\)-integrins from 6 to 20 weeks. In arteries from adult SHR, the volume density of collagen was significantly increased.\textsuperscript{55} Bézie et al\textsuperscript{50} have also reported increases in \(\alpha_v\)-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 \(\alpha_v\beta_3\), is one such extracellular component that may be important in vascular remodeling in hypertension. It co-localizes with proliferating SMCs in SHR\textsuperscript{92} 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 fibronectin\textsuperscript{90} and \(\alpha_v\beta_1\)-integrins\textsuperscript{50,55} 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 \(\alpha_v\beta_3\)-integrins,\textsuperscript{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 \(\alpha_v\beta_3\)-integrins.\textsuperscript{94} In vitro studies have demonstrated that osteopontin overexpression is associated with arterial SMC proliferation.\textsuperscript{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.\textsuperscript{27} In SHR resistance arteries, collagen density or relative content was normalized by ACE inhibition,\textsuperscript{55,56} \(\alpha_1\) receptor blockade,\textsuperscript{55} and the dihydropyridine \(\mathrm{Ca}^{2+}\)-channel blocker amlodipine.\textsuperscript{56} Aldosterone antagonism also reduced collagen in SHR aortae.\textsuperscript{96} Likewise, in vessels from SHR-sp and DOCASalt rats, \(\alpha_1\) receptor antagonism reduced collagen types I, III, and IV mRNA.\textsuperscript{63,97} 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.\textsuperscript{98} 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 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.

Acknowledgments

The authors’ work was supported by grants 13570 and 37917 and a group grant to the Multidisciplinary Research Group on Hypertension to E.L.S., all from the Canadian Institutes of Health Research (CIHR, previously Medical Research Council of Canada). H.D.I. was supported by a Centennial Fellowship (now entitled Senior Research Fellowship) from CIHR.

References


75. Benetos A, Lacolley P, Safar ME. Prevention of aortic fibrosis by spon-

76. Galis ZS, Muszynski M, Sukhova GK, Simon-Morrissey E, Unemori EN, Lark MW, Amento E, Libby P. Cytokine-stimulated human smooth muscle cells synthesize a complement of enzymes required for extra-


82. Galis ZS, Muszynski M, Sukhova GK, Simon-Morrissey E, Unemori EN, Lark MW, Amento E, Libby P. Cytokine-stimulated human smooth muscle cells synthesize a complement of enzymes required for extra-


89. Intengan HD, Schiffrin EL. Collagen degradation is diminished in mes-


96. Benetos A, Lacolley P, Safar ME. Prevention of aortic fibrosis by spon-


Vascular Remodeling in Hypertension: Roles of Apoptosis, Inflammation, and Fibrosis
Hope D. Intengan and Ernesto L. Schiffrin

_Hypertension_. 2001;38:581-587
doi: 10.1161/hy09t1.096249

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/3/581

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/