Over the past few years noninvasive and invasive techniques have allowed a better appreciation of vascular changes in hypertensive humans and experimental animals. Large arteries undergo outward hypertrophic remodeling and increased stiffness with aging, and in hypertension there may be an acceleration of this process leading to enhanced pulse pressure. A reduced aortic diameter in middle-aged hypertensive subjects may also play a role in increases in pulse pressure through increased specific impedance, contradicting the classic hypertensive aortic phenotype characterized by vascular wall degeneration and calcification and increased aortic diameter. In advanced hypertension, however, the elastic laminae undergo duplication and fragmentation, with increased deposition of collagen and fibronectin, contributing to increased stiffness.

Classically the remodeling of small arteries in hypertension has been associated with increased media thickness, but recent studies have demonstrated that 2 types of remodeling are found, inward eutrophic or inward hypertrophic remodeling, depending on whether the media cross-sectional area is enlarged (true hypertrophy). Although eutrophic remodeling is usually found in essential (primary) hypertension in humans and spontaneously hypertensive rats (SHRs); in secondary hypertension such as in renovascular hypertension, primary aldosteronism, or in pheochromocytoma; in hypertensive humans and rodents, which may be induced by ET, angiotensin (Ang) II, and aldosterone acting in an endocrine or paracrine fashion. The potential remodeling role of tissue transglutaminases that generate interactions of extracellular matrix fibrillar components with attachment sites on VSMCs has been reported recently. In the remodeled artery, with rearranged cellular and fibrillar components attributed to changes in interaction of these structures through integrins, collagen fibers are recruited at higher distending pressures in vessels that accordingly initially exhibit decreased stiffness, although later stiffness is enhanced. Low-grade inflammation of both the arterial wall and perivascular fat participates as well in arterial remodeling, characterized by inflammatory cell infiltration, upregulation of inflammatory mediators, such as vascular cellular adhesion molecule 1, intercellular adhesion molecule 1, nuclear factor (NF)-κB, monocyte chemoattractant factor 1, and plasminogen activator inhibitor 1, and enhanced oxidative stress.

Small artery remodeling may be the first manifestation of target organ damage in hypertension, because in our series of patients, 100% of stage I hypertensive subjects present small artery remodeling, whereas only 60% have endothelial dysfunction (see below), characterized by inflammatory cell infiltration, upregulation of inflammatory mediators, and decreased media thickness. Small artery structure was performed has demonstrated the prognostic significance of small artery remodeling, because hypertensive patients with the highest media:lumen ratio had increased incidence of cardiovascular events.

Dysfunction of the endothelium is often associated with elevation of blood pressure (BP) and may be a secondary phenomenon that does not initiate BP elevation; rather, it may be associated with cardiovascular risk factors that cluster with hypertension, such as smoking, obesity, dyslipidemia, metabolic syndrome, and diabetes mellitus. It may contribute to
atherosclerosis progression and events rather than BP elevation. Endothelial dysfunction may affect different functions of the endothelium and does not only manifest as reduced endothelium-dependent vasodilation. A dysfunctional endothelium will be characterized by an inflammatory phenotype of endothelial cells with increased proliferation, anoikis, altered morphology, production of C-reactive protein, and other inflammatory and thrombogenic mediators, including monocyte chemotactic protein 1 and plasminogen activator inhibitor 1, upregulated adhesion molecules, and enhanced thrombogenicity and adhesiveness for circulating cells.

Vascular Effects of Antihypertensive Therapy

Antihypertensive Therapy and Large Artery Stiffness

Antihypertensive agents may affect the vascular wall directly and indirectly, the latter resulting from effects of BP lowering. Reduction of BP shifts the wall to the more compliant segment of the stress/strain relationship, so that more elastin and less collagen determine vascular stiffness. Collagen linking to VSMCs and the degree of tensioning of the collagen jacket play important roles, because collagen contributes to stiffness of the vessel wall in the latter portion of the stress/strain curve, as collagen fibers may be coiled and not under tension until the VSMCs in series and elastin in parallel have been stretched.

Antihypertensive agents like calcium channel blockers (CCBs), Ang-converting enzyme inhibitors (ACEIs), Ang receptor blockers (ARBs), mineralocorticoid receptor antagonists, and nitrates may alter mechanical properties of conduit arteries. ACEIs, ARBs, mineralocorticoid receptor antagonists, and CCBs all decrease vascular stiffness. These effects may depend on the antifibrotic actions of these agents that downregulate the expression of transforming growth factor-β (TGF-β). Indeed, this has been well demonstrated for Ang II, which exerts its growth and profibrotic effects in part via stimulation of TGF-β, suggesting that at least ACEIs and ARBs, by inhibiting Ang II generation or blocking its action, may affect stiffness partly through this mechanism. Reduction of small artery stiffness decreases impedance, which delays wave reflection and consequently the augmentation of pulse pressure centrally in the aorta. β-Blockers, at least atenolol, do not appear to reduce vascular stiffness and by decreasing heart rate increase pulse pressure, which may explain their reduced effectiveness on events compared with renin-angiotensin system inhibitors in some clinical trials, such as the Losartan Intervention for Endpoint Reduction in Hypertension Study (LIFE trial). In these trials there are always small differences in BP control that leave open the question of whether these BP differences rather than effects attributable to the antihypertensive used explain the differential outcome.

Antihypertensive Therapy and Small Artery Structure

ACEIs, ARBs, and CCBs all decrease vascular stiffness. Changes in subcutaneous small arteries may reflect what happens in the coronary circulation, as shown by indirect measurements. Accordingly, a greater degree of small artery remodeling (media:lumen ratio) was associated with worse long-term cardiovascular outcomes. Benefit from blockade of the renin-angiotensin system was also demonstrated on small arteries from type 2 diabetic subjects. Interestingly, in diabetic persons, treatment with an ARB for 1 year resulted in upregulation of resistance artery Ang II type 2 receptors (AT₂R), which could improve vasodilatation. More recently, a selective Ang II type 2 receptor agonist, compound 21, reduced aortic or pericoronary collagen, small artery stiffness, and aortic superoxide generation and improved endothelial dysfunction in stroke-prone SHRs, particularly when associated with an ARB despite not lowering BP. Finally, the selective mineralocorticoid receptor antagonist eplerenone reduced stiffness of large and small arteries from hypertensive patients, explained by the reduction of collagen deposition and collagen elastin ratio in the vascular wall media. Neither remodeling nor endothelial function of small arteries improved under treatment with eplerenone despite BP normalization in this study.

Antihypertensive Therapy and Small Artery Function

The effects of ACEI on endothelial function measured by acetylcholine-induced relaxation (which is only one expression of endothelial function) are variable. Although short-term treatment with ACEIs failed to improve endothelial dysfunction measured in vivo, 2-year treatment with an ACEI slightly improved abnormal endothelium-dependent relaxation of small human arteries evaluated in vitro. Treatment with ARBs corrected endothelial dysfunction, as did CCBs, as did AT₂-receptor agonist, compound 21, reduced aortic or pericoronary collagen, small artery stiffness, and aortic superoxide generation and improved endothelial dysfunction in stroke-prone SHRs, particularly when associated with an ARB despite not lowering BP. Finally, the selective mineralocorticoid receptor antagonist eplerenone reduced stiffness of large and small arteries from hypertensive patients, explained by the reduction of collagen deposition and collagen elastin ratio in the vascular wall media. Neither remodeling nor endothelial function of small arteries improved under treatment with eplerenone despite BP normalization in this study.

Effect of Antihypertensive Treatment on Arterioles

Arterioles, with lumen diameters <100 μm, are an important site of vascular resistance. Larger arterioles undergo eutrophic remodeling in hypertension, as demonstrated in stroke-prone SHR pial arterioles. ACEI treatment was more effective than β-blockers in improving impaired cerebral vasodilatation in stroke-prone SHRs.
pressure in response to both types of agents have been implicated in these observations.

Rarefaction is another vascular change reported in experimental hypertension and in humans, characterized by a reduction in the density of very small arterioles. It results in 15% to 20% of the increase in peripheral resistance in hypertension, although its definitive impact remains to be established. Rarefaction may be functional and reversible or permanent (anatomic) with reduced arteriolar and capillary density. ACEIs improve rarefaction in experimental animals, which may result from reduction of Ang II levels and vasodilation. Ang II type 1 receptors (AT1R) have been implicated in the development of rarefaction through proapoptotic effects, whereas AT1R may participate in the vasodilata-

tion and correction of rarefaction. However, an antiangiogenic role of AT1R has been suggested by other authors, which may depend on the paradigm investigated. 

**Mechanisms of Vascular Remodeling Affected by Renin-Angiotensin-Aldosterone Inhibition**

The mechanisms whereby blockade of the renin-angiotensin system improves vascular structure and function probably result from inhibition of growth-promoting, pro-oxidant, and proinflammatory actions of Ang II. Vasodilatation has also been considered to play a role, because vasoconstriction may lead to small artery remodeling, and vasodilatation, through changes in flow, modulates vascular remodeling. Atenolol induces peripheral vasoconstriction, which could explain its inability to improve vascular remodeling, whereas agents that improve remodeling, like ACEIs, ARBs, or CCBs, are vasodilators.

Diminished activation of AT1R and their intracellular signaling, consequence of reduction of Ang II plasma levels by ACEIs or blockade of AT1R by ARBs, decreases intracellular calcium and activity of calcium-dependent kinases, such as Pyk-2, a focal adhesion kinase family member. NADPH oxidase activation decreases, with less generation of reactive oxygen species, decreased platelet-derived growth factor and epidermal growth factor receptor transactivation, and, subsequently, diminished activity of the mitogen activated protein kinases (MAPK), including extracellular signal-regulated kinase (ERK) 1/2, p38 MAPK, MAPK-activated protein kinase 2, and c-Jun N-terminal kinase (JNK), as well as Janus Kinase/Signal Transducer and Activator of Transcription, as depicted in the Figure. Reduced nuclear translocation of mediators, and activation of proto-oncogenes (c-fos, c-jun, and c-myc) and other transcription factors, leads to reduced growth of VSMCs and remodeling. The inflammatory response induced by Ang II is reduced, with diminished activation of NF-κB and adhesion molecule expression and less attraction of leukocytes into the vascular wall. Together with reduced TGF-β stimulation and fibrosis, blunting of oxidative stress and inflammation by these agents contributes to regression of remodeling of the vasculature. Similar effects to those elicited by Ang II may result from mineralocorticoid receptor (MR) activation by aldosterone. Using small interfering RNA we demonstrated in mouse VMSCs (which have 2 AT1R subtypes, AT1aR and AT1bR) that some of these actions, such as stimulation by aldosterone of ERK 1/2 and JNK, require a functional AT1aR, whereas NF-κB phosphorylation requires a functional AT1aR and AT1bR. Ang II stimulation of NF-κB phosphorylation requires a functional MR. Nuclear translocation of NF-κB requires AT1aR, AT1bR, and MR in response to aldosterone or Ang II, whereas aldosterone-induced c-fos gene transcription requires AT1aR. We recently confirmed these in vitro findings in vivo. Deficiency in agrtla prevented aldosterone-induced mesenteric resistance artery hypertrophic remodeling and endothelial dysfunction in mice.

**Mechanisms of Vascular Remodeling Beyond the Renin-Ang-System**

**ET Effects on Vascular Remodeling**

As already alluded to, we have studied the role of ET-1 in experimental and human hypertension. We first showed that salt-sensitive hypertensive models, such as deoxycorticosterone acetate-salt rats, have enhanced ET-1 expression in the endothelium, associated with hypertrophic remodeling and endothelial dysfunction that could be corrected by ET antagonists. We demonstrated with this study and by inducing deoxycorticosterone acetate-salt hypertension in SHRs that ET-1 has direct hypertrophic effects on the vasculature, particularly small arteries, and that hypertrophic remodeling is a signature of involvement of ET in the hypertensive process. Aldosterone infusion also increased ET-1 expression and induced hypertrophic vascular remodeling with ECM deposition of collagen types I and III and fibronectin. Indeed, other investigators have demonstrated that aldosterone modulates the promoter of ET-1 gene. Severe elevation of BP seems to trigger the expression of ET-1 in the endothelium, and, thus not surprisingly, patients with stage 2 primary hypertension exhibited increased expression of preproET-1 mRNA in the endothelium of small arteries from biopsies of gluteal subcutaneous tissue. To test vascular effects of ET-1, we generated a mouse that overexpressed human preproET-1 in the endothelium (eET-1 mouse) using the Tie-2 endothelium-specific promoter, and although BP was not elevated, small arteries exhibited hypertrophic remodeling and endothelial dysfunction, enhanced NADPH oxidase-derived reactive oxygen species, and upregulation of inflammatory mediators. Exposed to a high-salt diet, eET-1 mice presented a greater increase in BP compared with wild-type mice. High-salt diet exaggerated the endothelial dysfunction and oxidative stress. ET antagonism partially improved the effects of high-salt diet, whereas ET antagonism worsened them. Vascular gene expression profiling of eET-1 mice with DNA microarrays demonstrated increases in the expression of lipid metabolism genes, 4 of which were validated by quantitative PCR (cyp51, dgat2, scd1, and elov6), supporting a role for ET-1 in atherosclerosis. When eET-1 mice were crossed with atherosclerosis-prone apolipoprotein E−/− mice and fed a high-fat diet, lipid-containing plaques in eET-1/apolipoprotein E−/− crossed mice increased dramatically more than in apolipoprotein E−/−, associated with increases in BP. This suggests that increased endothelial ET-1 expression accelerates the progression of atherosclerosis and could link atherosclerosis and hypertension.
Obesity, Metabolic Syndrome, and Diabetes Mellitus

Together with Italian colleagues, we demonstrated that severely obese individuals exhibit hypertrophic small artery remodeling despite being normotensive. To further investigate vascular remodeling in the metabolic syndrome, we examined New Zealand Obese (NZO) mice, a metabolic syndrome model, which has insulin resistance, hyperinsulinemia, and slight BP elevation compared with New Zealand Normal (NZN) mice. We found that NZO mice exhibit increased hypertrophy of small arteries, with enhanced NADPH oxidase activity and expression of markers of vascular inflammation. These changes are associated with increased expression of angiotensin II type 1 receptors (AT1R) and decreased expression of angiotensin II type 2 receptors (AT2R), which are involved in regulating growth and inflammation in the vasculature.

Figure. Small artery remodeling may be eutrophic when medial/lumen ratio is enhanced but media cross-sectional area is not, or hypertrophic, when both are increased. In both forms, when lumen is reduced, the remodeling is called inward remodeling. In the presence of genetic predisposition and unfavorable environmental conditions (eg, excess salt), the brain through activation of the sympathetic nervous system will induce small rises in blood pressure (BP) that may generate damage-associated molecular patterns (DAMPs), which, when recognized by pattern-recognition receptors (PRRs), activate innate immunity, and through generation of neoantigens, may also activate adaptive immunity. Whether infectious agents acting through pathogen-associated molecular patterns (PAMPs) recognized by toll-like receptors (TLRs) also contribute to activation of immune response remains unclear. Breaking the balance between T-effector and T-regulatory lymphocytes leads to an inflammatory response that contributes to vascular remodeling. At the same time, BP elevation directly affects remodeling of blood vessels by increasing media stress and stimulation of mechanoreceptors. It may also stimulate oxidative stress in the vascular wall by enhancing NADPH oxidase activity. Remodeling of the wall is importantly affected by angiotensin (Ang) II, which stimulates calcium release leading to vasoconstriction that may become embedded as deposition of extracellular matrix occurs, also under the influence of Ang II. Ang II–induced vasoconstriction also acts via Rho kinase (ROCK), which increases myosin light chain (MLC) sensitivity to calcium. Growth, inflammation, and repair processes interact with vasoconstriction to contribute to remodeling. Ang II enhances all of the stages of the inflammatory response: vascular permeability through prostaglandins and vascular endothelial growth factor (VEGF); leukocyte recruitment and activation through selectins, integrins, adhesion molecules, cytokines, and chemokines; and vascular repair processes through mediators of cell growth and fibrosis. Ang II–induced vascular inflammation is mediated through modulation of vascular wall effectors by Ang II type 1 receptors (AT1,R), which are proinflammatory, and Ang II type 2 receptors (AT2,R), which are anti-inflammatory. EGFR indicates epidermal growth factor receptor; ERK, extracellular regulated kinase; JNK, c-Jun N-terminal kinase; MAPK, mitogen activated protein kinase; MK2, MAPKAP kinase-2; MAPK activated protein kinase-2; MLCK, MLC kinase; MMP, matrix metalloprotease; TGF-β, transforming growth factor-β; TIMP, tissue inhibitor of MMP.
black control mice. Mesenteric resistance arteries from NZO mice had hypertrophic vascular remodeling and impaired endothelium-dependent relaxation to acetylcholine. The antioxidant Tempol improved the latter, suggesting reduced NO bioavailability attributed to enhanced oxidative stress. Dimer:monomer ratio of endothelial NO synthase was decreased in NZO mice, which suggested endothelial NO synthase uncoupling, and superoxide and peroxynitrate were increased, as well as adhesion molecule expression. Significantly increased NADPH oxidase activity and superoxide generation and adipocyte hypertrophy, associated with inflammatory cell infiltration, enhanced tumor necrosis factor-α expression, and diminished adiponectin production, were found in perivascular adipose tissue of NZO mice. Norepinephrine-induced vasoconstriction was reduced in the presence of perivascular adipose tissue from New Zealand black mice but unaffected by perivascular adipose tissue from NZO mice, suggesting that NZO perivascular adipose tissue had less anticontractile properties, which may be linked to the deficiency in adiponectin.

In previous studies we showed in rats that peroxisome proliferator activator receptor (PPAR)α and PPARγ agonists protected vessels from growth-promoting, inflammatory, and oxidant effects of Ang II. To test the hypothesis that PPARγ counteracts Ang II–induced vascular remodeling and endothelial dysfunction, we generated a model of inducible VSMC-selective PPARγ gene deletion by crossing PPARγ floxed mice with mice expressing tamoxifen-inducible Cre recombinase under control of the smooth muscle myosin heavy chain promoter. Inducing PPARγ gene disruption in VSMCs exacerbated Ang II–induced vascular remodeling and endothelial dysfunction via enhanced vascular oxidative stress and inflammation, revealing a protective role of VSMC PPARγ that could be important as a therapeutic target in cardiometabolic disease.

Immunity and Vascular Remodeling

Low-grade inflammation is increasingly recognized as a mechanism of vascular injury and BP elevation. It is unclear how inflammation and immune mechanisms are activated in hypertension. In the presence of genetic predisposition and unfavorable environmental conditions (excess salt?), the brain, through activation of the sympathetic nervous system, will induce small rises in BP. The BP rise could generate damage-associated molecular patterns recognized by pattern-recognition receptors that activate innate immunity and also neoantigens that could activate adaptive immunity. Whether infectious agents acting through pathogen-associated molecular patterns recognized by toll-like receptors also contribute to activation of immune responses remains unclear. Breaking the balance between T-effector and T-regulatory lymphocytes leads to an inflammatory response that contributes to vascular remodeling (Figure).

To determine whether innate immunity played a role in vascular disease and hypertension we studied the osteopetrotic mouse, which has a mutation in the monocyte/macrophage colony stimulating factor (mcsf) gene, and exhibits monocyte and macrophage deficiency. Ang II infusion or deoxycorticosterone acetate-salt failed to induce vascular remodeling, endothelial dysfunction, or elevate BP in homozygous mcsf0/0 mice, whereas in heterozygous mcsf0/+ mice the effects were intermediate, demonstrating a role of innate immunity in vascular remodeling. These results have been extended recently by Wenzel et al. who demonstrated that depletion of lysozyme M-positive (LysM−) myelomonocytic cells by low-dose diphtheria toxin in mice with inducible expression of diphtheria toxin receptor (LysMIDTR mice) prevented Ang II–induced vascular dysfunction, endothelial dysfunction, and BP elevation.

Adaptive immunity has also been implicated in vascular damage in hypertension. A blunted Ang II–induced BP rise, aortic and small artery remodeling, and vascular oxidative stress in rag1−/− mice, deficient in T and B lymphocytes, could be corrected by adoptive transfer of effector T cells from control mice. In Id2−/− mice that have a deficit in Langerhans and splenic CD8a+ dendritic cells, decreased natural killer cells, and altered CD8 T-cell memory, Ang II pressor responses were blunted. T-helper 17 lymphocytes may play a role in response to Ang II, as shown by less-persistent BP elevation, less T-cell infiltration in perivascular fat, and superoxide production in aortic rings in Ang II–infused IL17−/− mice.

We have suggested that salt-sensitive hypertension may have enhanced adaptive immunity arising from genetic predisposition with loci on chromosome 2, which bears many proinflammatory genes, such as vascular cellular adhesion molecule-1, interleukin (IL) 2, IL-6 receptor, fibroblast growth factor 2, and AT1bR. We studied Dahl salt-sensitive hypertensive rats, and consomic rats (SSBN2) bearing chromosome 2 from normotensive Brown Norway rats on a Dahl salt-sensitive genetic background. The consomic strain had less vascular inflammation and remodeling, particularly in response to high salt intake, associated with upregulation of CD4+CD25+ and CD8+CD25+ lymphocytes (T-regulatory lymphocytes [Treg]) and their activity, Foxp3 expression (Treg prototypical transcription factor), and enhanced production of the anti-inflammatory mediators IL-10 and TGF-β by Treg. Treg in the vasculature of Dahl salt-sensitive rats expressed low levels of Foxp3 and did not produce TGF-β and IL-10 but demonstrated upregulation of inflammatory cytokines (IL-1β, IL-2, IL-6, tumor necrosis factor-α, and interferon-γ). More recently we found that Ang II–infused mice subjected to adoptive transfer of Treg from untreated mice presented lower telemetric systolic BP, reduced small artery stiffness, decreased generation of superoxide and immune cell infiltration in vascular and perivascular tissue, and decreased impairment of endothelial function. Aldosterone induces effects similar to Ang II, with the addition that hypertrophic remodeling could be corrected by adoptive transfer of Treg from untreated mice and that there was no BP effect. The correction of vascular injury by Treg adoptive transfer in the absence of BP changes in aldosterone/salt mice suggests that the effects found may be independent of hemodynamics and could be mediated partly through anti-inflammatory actions of IL-10.

Conclusions

The role of different mechanisms associated with remodeling of vessels in hypertension, metabolic disease, and other forms
of cardiovascular disease has increasingly been elucidated. Some of these mechanisms may allow identification of novel biomarkers and new targets for new therapies to treat hypertension and other cardiovascular diseases. We hope that our present knowledge will stimulate new research, which will lead to novel approaches that will improve outcomes by reducing end-organ damage.

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References


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