Vascular Remodeling in Hypertension
Mechanisms and Treatment
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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 fetal (EIIIA) 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 hyper- tension associated with diabetes mellitus; and in acromegaly, hypertrophic remodeling has been described. In mineralocorticoid hypertension in rodents and in salt-sensitive Dahl rats, in both of which the endothelin (ET) system is activated, remodeling of small arteries is also hypertrophic (see below). Thus, when the renin-angiotensin system is even mildly activated (primary hypertension and SHRs), remodeling is usually eutrophic. In salt-dependent hypertension, diabetes mellitus, and malignant hypertension, all conditions in which the ET system is activated, remodeling is hypertrophic. Hyperplasia of vascular smooth muscle cells (VSMCs) is found in small arteries of hypertensive rats, whereas in the aorta, VSMC hypertrophy has been reported. In essential hypertension, cell volume and number in small arteries are similar to those of normotensive subjects. The mechanisms leading to inward eutrophic remodeling are poorly understood but could result from inward growth combined with peripheral apoptosis or from vasoconstriction embedded in an expanded extracellular matrix. Indeed, there is deposition of collagen and fibronectin with increased collagen:elastin ratio in small vessels from 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 (see below), 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) and 45% left ventricular hypertrophy. Follow-up of patients in whom investigation of small artery structure was performed has demonstrated the diagnostic 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
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 elastic and less collagen determine vascular stiffness. Collagen linking to VSMCs and the degree of tensing 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. 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 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 endothelin-dependent relaxation of small human arteries evaluated in vitro. Treatment with ARBs corrected endothelial dysfunction, and as did CCBs. Blockade with atenolol failed to improve endothelial function in several studies, and ARBs normalized endothelial function in early type 2 diabetes mellitus. However, in advanced type 2 diabetes mellitus with hypertension, an ARB added to previous antihypertensive therapy, including ACEIs and CCBs, did not have beneficial effects on the endothelium despite the fact that structure was partially corrected. Mechanisms in the media of blood vessels and endothelium affected by these agents could be different. Alternatively, endothelial dysfunction could be more resistant to improvement even in the presence of lower BP and antihypertensive agents. The different NADPH oxidases (nox1, nox2, and nox4) and their subunits in VSMCs and endothelium may be involved in the differential effects of antihypertensive drugs. Generation of vasodilator hydrogen peroxide in the endothelium is another mechanism that differentiates endothelial reactive oxygen species and VSMC-generated free radicals, as is endothelial heme-oxygenase 1 that generates carbon monoxide, another vasodilator.

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. Changes in local pulse...
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.69 Rarefaction may be functional and reversible or permanent (anatomic) with reduced arteriolar and capillary density. ACEIs improve rarefaction in experimental animals,70 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 AT2R may participate in the vasodilation and correction of rarefaction.71 However, an antiangiogenic role of AT2R has been suggested by other authors, which may depend on the paradigm investigated.72

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.73 Vasodilatation has also been considered to play a role,74 because vasoconstriction may lead to small artery remodeling.21 and vasodilatation, through changes in flow, modulates vascular remodeling.75 Atenolol induces peripheral vasoconstriction,76 which could explain its inability to improve vascular remodeling,43–49 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 2,77 and c-Jun N-terminal kinase (JNK), as well as Janus Kinase/Signal Transducer and Activator of Transcription,73,78 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 AT1R and AT1bR.79 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 agtrla prevented aldosterone-induced mesenteric resistance artery hypertrophic remodeling and endothelial dysfunction in mice.80

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,81 associated with hypertrophic remodeling and endothelial dysfunction that could be corrected by ET antagonists.14 We demonstrated with this study and by inducing deoxycorticosterone acetate-salt hypertension in SHRs82 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.15 Aldosterone infusion also increased ET-1 expression and induced hypertrophic vascular remodeling with ECM deposition of collagen types I and III and fibronectin.74 Indeed, other investigators have demonstrated that aldosterone modulates the promoter of ET-1 gene.83 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.84 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,85 enhanced NADPH oxidase–derived reactive oxygen species, and upregulation of inflammatory mediators.86 Exposed to a high-salt diet, eET-1 mice presented a greater increase in BP compared with wild-type mice.87 High-salt diet exaggerated the endothelial dysfunction and oxidative stress. ETA antagonism partially improved the effects of high-salt diet, whereas ETA antagonism worsened them. Vascular gene expression profiling of eET-1 mice with DNA microarrays demonstrated increases in the expression of lipid metabolism genes,88 4 of which were validated by quantitative PCR (cyp51, dgat2, scd1, and elov6), supporting a role for ETA in atherosclerosis. When ET-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

Figure. Small artery remodeling may be eutrophic when media/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 pattern-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 be 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 (AT1R), which are proinflammatory and Ang II type 2 receptors (AT2R), which are anti-inflammatory and 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.
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had less anticontractile properties, which may be linked to the

deficiency in adiponectin.90,91

In previous studies we showed in rats that peroxisome

proliferator activator receptor (PPAR)α92 and PPARγ agonists93

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 deletion94 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.95 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

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remodeling (Figure).

To determine whether innate immunity played a role in

vascular disease and hypertension we studied the osteopetro-
tropic mouse, which has a mutation in the monocyte/macro-

phage colony stimulating factor (mcsf) gene, and exhibits

monocyte and macrophage deficiency. Ang II infusion96 or
deoxyxorticosterone acetate-salt97 failed to induce vascular

remodeling, endothelial dysfunction, or elevate BP in ho-

mozygous mcsf+/− mice, whereas in heterozygous mcsf+/−/− mice

the effects were intermediate, demonstrating a role of innate

immunity in vascular remodeling. These results have been

extended recently by Wenzel et al.98 who demonstrated

that depletion of lysozyme M-positive (LysM−) myelomonocy-
cytic cells by low-dose diphertheria toxin in mice with induc-
able expression of diphertheria toxin receptor (LysMiDTR

mice) prevented Ang II–induced vascular dysfunction, endo-
thelial 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,99

could be corrected by adoptive transfer of effector T cells

from control mice. In Il2−/− mice that have a deficit in

Langerhans and splenic CD8α+ dendritic cells, decreased

natural killer cells, and altered CD8 T-cell memory, Ang II

pressor responses were blunted.100 T-helper 17 lymphocytes

could play a role in response to Ang II.101 as shown by

less-persistent BP elevation, less T-cell infiltration in perivas-
cular 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 pre-
disposition 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.102 We studied Dahl salt-sensitive

hypertensive rats, and consomic rats (SSBN2) bearing chro-

mosome 2 from normotensive Brown Norway rats on a Dahl

salt-sensitive genetic background. The consomic strain had

less vascular inflammation and remodeling,103 particularly in

response to high salt intake,104 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 Foxp3β 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, re-
duced small artery stiffness, decreased generation of super-
oxide and immune cell infiltration in vascular and perivascu-
tary tissue, and decreased impairment of endothelial

function.105 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.106 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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