This study reviews recent experimental data from our own and other laboratories on the effects of hypertension on the arterial wall and the potential mechanisms by which hypertension can induce vascular injury and accelerate atherosclerosis. The findings suggest that the responses of the arterial media to hypertension reflect appropriate adaptations to increased intramural tension with resultant medial thickening secondary to an increase in both cellular mass and extracellular matrix. The role of growth factors in this process and their effects on arterial contractility are discussed as well as the potential importance of the changes in extracellular matrix constituents. The intimal changes induced by hypertension have many similarities to those caused by aging or hypercholesterolemia and can in part reflect general arterial responses to injury. They make the arterial wall more vulnerable to the effects of hypercholesterolemia, however, and as noted in our studies with the Watanabe heritable hyperlipidemic rabbit, pronounced acceleration of atherosclerosis is induced when hypertension is combined with hypercholesterolemia. Antihypertensive drugs can affect the arterial response to hypercholesterolemia. In the present study, new data are provided indicating that captopril inhibits aortic atherosclerosis in the Watanabe heritable hyperlipidemic rabbit in association with a pronounced reduction in cellularity of lesions. (Hypertension 1990;15:666–674)

Hypertension can cause major changes in the arterial wall. Some of these are protective in nature and are associated with a remodeling of the artery to better withstand the increase in wall tension resulting from the elevated intravascular pressure. Other responses to vascular injury caused by hypertension, however, can predispose the artery to further adverse consequences. In this study, I will discuss the nature of these responses in the arterial media and intima and the mechanisms potentially responsible for these alterations.

Changes in the Arterial Media with Hypertension

Cellular Responses

The medial layer normally constitutes most of the thickness of an artery. During growth and development, paralleling the rise in blood pressure, there is a rapid increase in the number of medial smooth muscle cells (SMCs) and their organization into lamellar units. When comparing adults of different species, the number of lamellar units and the overall wall thickness reflect the size of the animal and the diameter of the vessel.1 The calculated tension per lamellar unit is relatively constant throughout a wide range of species and vessel sizes. Hypertension causes an increase in thickness in the arterial media (Figure 1) that serves to counteract the rise in wall tension.

The lamellar units of the arterial media are composed of SMCs and connective tissue components such as collagen, elastin, proteoglycans, and fibronectins. With hypertension, the number of lamellar units remains relatively constant, and increases in wall thickness are achieved by changes in both cellular mass and connective tissue content.2 Previous studies including those by Owens and Schwartz3,4 as well as ourselves5 have demonstrated that in most rat models of hypertension, SMC hypertrophy, which can be associated with nuclear polyplody, is the reason for the major increase in SMC mass. This might not be a uniform response, however, because in the rat with aortic coarctation, hyperplasia without hypertrophy or polyplody of arterial SMCs can occur.6

Although the stimulus for arterial SMC growth as a result of hypertension is uncertain, studies involving cultured SMCs have been of considerable interest. Various vasoactive agents including catechol-
amines\textsuperscript{7} and angiotensin II\textsuperscript{6} have reportedly stimulated growth of arterial SMCs. The angiotensin II effect can be seen with concentrations as low as $10^{-9}$ M and is associated with increases in cell size and protein content without an effect on cell number. The hypertrophy of the cultured SMCs caused by angiotensin II is associated with increased expression of the $\alpha$-chain of platelet-derived growth factor (PDGF) and of the proto-oncogene $c$-myc.\textsuperscript{9} Transforming growth factor-$\beta$ (TGF-$\beta$) also appears to stimulate the development of SMC hypertrophy and polyploidy in culture.\textsuperscript{10}

Our recent work in this area has been concerned primarily with the investigation of the effects of hypertension on the expression of growth factors in rat aorta. Although the in vivo experimental systems are more complex and the data are more difficult to interpret than with cell culture studies, there is an obvious need to study the problems in intact animals and to determine the relevance of the in vitro findings to the hypertensive state. We have demonstrated the expression in rat aorta of several growth factors including epidermal growth factor (EGF), insulin growth factors I and II, acidic and basic fibroblast growth factors, TGF-$\beta$ 1, and both chains of PDGF.\textsuperscript{11} We also have found that deoxycorticosterone (DOC)-salt hypertension caused an increase in aortic TGF-$\beta$ 1 expression of approximately threefold (Figure 2), although the expression of the other growth factors remained unchanged. Recently R. Cohen of our group has observed that TGF-$\beta$ 1 stimulates contractility of arterial rings (personal communication, 1989). The latter findings are interesting because TGF-$\beta$ is a polypeptide that appears to be involved in tissue inflammation and repair.\textsuperscript{12} It is carried in platelets and released in areas of injury. It is a potent chemoattractant for macrophages and can stimulate the production of collagen, fibronectins, and proteoglycans.\textsuperscript{13,14} It could therefore play a role in mediating some of the vascular responses to hypertension.

Although our data on arterial growth factors have as yet only involved measurement of steady-state levels of messenger RNA (mRNA) and not actual concentrations of growth-promoting proteins, it is reasonable to suggest that hypertension influences arterial SMC growth by affecting the balance between growth factors in a manner that would determine whether the cells divide, differentiate, or undergo hypertrophy. Several potential sources for the growth factors might be present. As already suggested, they could be produced in the vascular cells themselves and act through autocrine or paracrine effects. They could also, however, originate from blood-borne cells that penetrate the arterial wall (see further discussion) or from other blood constituents that could have increased entry into the artery as a result of the hypertension.

Several growth factors including PDGF\textsuperscript{15} and EGF\textsuperscript{16} have reportedly induced arterial vasoconstriction, and several vasoconstrictor agents including angiotensin II,\textsuperscript{8} $\alpha$\textsubscript{1} receptor agonists,\textsuperscript{7} endothelin,\textsuperscript{17} and serotonin\textsuperscript{18} stimulate growth of cells in culture. These common effects appear to be mediated through increases in intracellular $Ca^{2+}$, which is involved in both growth and contraction. The mechanisms for the rises in intracellular $Ca^{2+}$ appear complex, however, and can differ with different growth factors. For example, for PDGF, phospholi-
pressure (BP) from each group of rats is shown at the bottom
Northern blot hybridization analysis of aortic RNA from
normotensive and hypertensive rats. Twenty micrograms of
expression in aorta of normotensive and hypertensive rats.

av.systolic BP
(mmHg)
control
DOC-salt control
DOC-salt
DOC.salt
125
116
174
191
191

FIGURE 2. Transforming growth factor-β (TGF-β) gene
expression in aorta of normotensive and hypertensive rats.
Northern blot hybridization analysis of aortic RNA from
normotensive and hypertensive rats. Twenty micrograms of
total RNA was applied to each lane. Average systolic blood
pressure (BP) from each group of rats is shown at the bottom
of each lane. Top panel: TGF-β gene expression. (—) endo-
theelial control, RNA extracted from endothelium-scraped aortas
of untreated rats. Deoxycorticosterone-salt (DOC/salt) groups
were all treated for 3 weeks (2-day exposure time). Bottom
panel: β-Actin gene expression. Same blot previously hybrid-ized
with human TGF-β complementary DNA (cDNA) probe
was rehybridized with a rat β-actin cDNA probe (3-hour
exposure time). Reproduced with permission.14

pase C activation and phosphoinositide hydrolysis can be
involved,19 whereas for EGF, an effect on prostaglandins can be important.20 Both PDGF and angio-
tensin II appear to stimulate the Na⁺-H⁺ exchange
system in cells leading to an increase in intracellular
Na⁺.19,21 Because a Na⁺-Ca²⁺ exchange mechanism
also appears to be present in SMCs,22 an increase in
SMC Na⁺ could reduce the rate of Ca²⁺ efflux from
the cell, causing an increase in intracellular calcium. A
detailed discussion of this topic is outside the scope of
the present study but can be obtained from an excellent
recent review of the subject.19

**Extracellular Matrix Changes**

The SMCs of the arterial media are encircled by a
dense network of connective tissue. Recent data
suggest that the organization of connective tissue
might be influenced by a complex family of receptor
proteins called integrins, which bind specifically to
individual connective tissue components.23 Experimental
hypertension causes an increase of arterial
collagen, elastin, and proteoglycans.24,25 presumably
as a result of stimulation of their production by SMCs.
The rise in collagen and elastin is approximately pro-
portionate to the increase in arterial weight.25

Another set of connective tissue proteins receiving
considerable recent attention that have not been
studied in hypertension are the fibronectins. These
large glycoproteins with a molecular weight of
approximately 500,000 are composed of two subunits
with repeating sequences that bind fibrinogen, hepa-
rin, and collagen.26 In the artery, fibronectins are
present in the subendothelial space, media, and
adventitia.27 After balloon-catheter injury, the distrib-
ution of the different forms of fibronectin appears
altered together with the phenotypic expression of
SMCs.28 Fibronectins are also reportedly involved in
many important cellular functions that are relevant
to our current discussion including cell adhesion,
differentiation, growth, and motility, as well as
thrombosis and wound healing.29 The modulation of
proliferation of cultured SMCs by TGF-β appears
related to an increase in fibronectin synthesis and can
be mimicked by addition of soluble fibronectin to the
culture.30 TGF-β has also reportedly increased
expression of fibronectin and of both units of the
fibronectin receptor in lung fibroblasts.31

We recently have initiated studies on the influence
of experimental hypertension on fibronectin expres-
sion in rat aorta. We have measured steady-state
mRNA levels of fibronectin by Northern blot analysis
and have shown a substantial rise in fibronectin gene
expression after 2 weeks of DOC-salt administration
(1. Takasaki, unpublished observations). Similar
results have been obtained after 6 days of angiotensin
II infusion by Alzet minipump (Alza Corp., Palo Alto,
California). Thus, elevation in blood pressure can
cause changes in arterial fibronectins that could pos-
sibly alter cell growth and other arterial responses.

**Effects of Hypertension on the Arterial Intima**

The intimal changes induced by hypertension can
initially be adaptive in nature but ultimately can
predispose the vasculature to further damage.

**Endothelial Alterations**

Extensive endothelial abnormalities can be associ-
ated with hypertension. Soon after induction of
DOC-salt hypertension, the endothelium will show
changes in the shape of cells and an increase in their
number.32,33 The latter can reflect a response to the
increase in arterial diameter that leads to an augmen-
tation in endothelial surface area. Functional abnor-
malities of the endothelium also can occur. Recently,
several groups have reported that endothelium-
dependent relaxation of the arterial wall is dimin-
ished in hypertensive as compared with normotensive
animals (for review, see Reference 34). Additionally,
intimal permeability to a number of substances
including horseradish peroxidase, colloidal carbon,
albumin, and lipoproteins can also be increased by
hypertension.35-37

SMCs and blood-borne cells accumulate in the sub-
endothelial space in response to hypertension. In the
DOC-salt model, such accumulation is preceded by a
pronounced increase in adherence to the endothelial
surface of blood-borne monocytes, lymphocytes, and granulocytes (Figure 3).32 Platelet adherence to the intima is not typically present and neither is endothelial cell loss. We have observed increased motility of SMCs out of aortic explants obtained from hypertensive animals38 and increased growth potential of such cells.38,39 If similar changes also occur in vivo, then hypertension might stimulate medial SMCs to migrate into the intima where they could proliferate and contribute to the development of intimal thickening.

Many of the intimal changes caused by hypertension are broadly similar to those observed with aging or hypercholesterolemia.37,40–43 These include endothelial cell and SMC proliferation, increased perme-

**Figure 3.** Scanning electron photomicrographs of descending thoracic aorta in 16-week-old Wistar-Kyoto rats. Top panel: Illustrates findings in a control rat. Note relatively flat and uniform luminal surface without evidence of adhering cells. Bottom panel: Photomicrograph of rat aorta after 4 weeks of deoxycorticosterone (DOC)-salt treatment. Note irregular surface with several blood cells adhering to it. Original magnification, ×1,000 top panel; ×1,500 bottom panel.

**Table 1.** Comparisons Between Arterial Intimal Changes Associated With Hypertension, Aging, and Atherosclerosis

<table>
<thead>
<tr>
<th>Intimal abnormalities</th>
<th>Hypertension</th>
<th>Aging</th>
<th>Hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC shape changes</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reduced EC-derived relaxation</td>
<td>+</td>
<td>...</td>
<td>+</td>
</tr>
<tr>
<td>Endothelial permeability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Leukocyte adherence</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macrophage accumulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SMC migration</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SMC proliferation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Proteoglycans accumulation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Intimal thickening</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lipid accumulation</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Atherosclerotic plaque</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
</tbody>
</table>

EC, endothelial cell; SMC, smooth muscle cell; +, present; 0, absent.
In various experimental models of hypertension and in hypertensive humans, atherosclerotic lesions are uncommon when plasma lipoprotein levels are low. The intimal changes previously described lead to thickening of the intima but do not generally progress to atherosclerotic plaque formation. That plasma lipoproteins play a key role in determining the intimal response to hypertension has been demonstrated in our recent studies involving the Watanabe heritable hyperlipidemic (WHHL) rabbit, which has a genetic defect in cellular receptors for low density lipoproteins (LDL). Induction of one-kidney, one clip hypertension in these rabbits for periods as brief in length as 3 months caused a pronounced increase in extent and severity of atherosclerosis in the aorta (Table 2 and Figure 4). We have also observed atherosclerotic lesions of the proximal coronary arteries, left ventricular hypertrophy, and patchy areas of myocardial cell loss in the hypertensive WHHL rabbit. The model therefore might be useful for studies of the effects of left ventricular hypertrophy on cardiac function and myocardial perfusion in the presence of coronary atherosclerosis.

### Effects of Antihypertensive Drugs

Several antihypertensive drugs, particularly β-blockers and calcium antagonists, have inhibited atherogenesis in normotensive cholesterol-fed animals. The mechanism of effect of any of these agents remains unknown, although an obvious feature common to all of these drugs is their ability to lower blood pressure or alter hemodynamic stresses on the arterial wall.

<table>
<thead>
<tr>
<th>Aortic region</th>
<th>Control</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total aorta</td>
<td>16±3</td>
<td>77±4*</td>
</tr>
<tr>
<td>Ascending and arch</td>
<td>47±15</td>
<td>99±1†</td>
</tr>
<tr>
<td>Descending thoracic</td>
<td>6±1</td>
<td>89±5*</td>
</tr>
<tr>
<td>Abdominal</td>
<td>15±2</td>
<td>37±11</td>
</tr>
</tbody>
</table>

Values are percentage of intimal surface (mean±SE). *p<0.001, values represent mean±SE. †p=0.02, adapted from Reference 45.

### Table 3. Effects of Captopril on Aortic Surface Atherosclerosis in Watanabe Heritable Hyperlipidemic Rabbits

<table>
<thead>
<tr>
<th>Aortic region</th>
<th>Control</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total aorta</td>
<td>47.9±3.6</td>
<td>29.7±3.9*</td>
</tr>
<tr>
<td>Ascending and arch</td>
<td>76.3±4.3</td>
<td>76.3±3.7</td>
</tr>
<tr>
<td>Descending thoracic</td>
<td>48.9±5.2</td>
<td>15.3±3.9†</td>
</tr>
<tr>
<td>Abdominal</td>
<td>28.6±2.5</td>
<td>26.2±4.4</td>
</tr>
</tbody>
</table>

Values are percentages of intimal surface (mean±SE). *p<0.01, values represent mean±SE. †p<0.001, adapted from Reference 54.
FIGURE 5. Top panel: Cross-section through atherosclerotic plaque in descending thoracic aorta of 12-month-old control Watanabe heritable hyperlipidemic (WHHL) rabbit. This area was evaluated visually as an "advanced lesion." Note cellularity of the intimal lesion and thickness of the media. Bottom panel: Cross-section through an "advanced lesion" in a 12-month-old WHHL rabbit after 9 months of captopril treatment. Note sparse cellularity of the intima and the thinner media than shown in top panel. Both sections were stained with hematoxylin-eosin (original magnification, ×100).

contrast to their favorable effects in inhibiting atherosclerosis associated with cholesterol-feeding, however, propranolol, nifedipine, and verapamil have failed to influence atherogenesis in the WHHL rabbit.

Because of the effects of angiotensin II on SMC growth as previously discussed and our interest in evaluating the action of antihypertensive therapy on the arterial wall, we recently performed a study to
examine the long-term effects of the angiotensin converting enzyme (ACE) inhibitor captopril on aortic atherosclerosis in the normotensive WHHL rabbit. Captopril was added to the diet in doses adequate to reduce serum ACE activity, and treatment was maintained for 3–12 months of life. A significant reduction in aortic atherosclerosis was observed in the captopril-treated rabbits as compared with control WHHL rabbits with the major inhibition occurring in the descending thoracic aorta (Table 3). Intimal cholesterol content was also reduced markedly in this region. The changes were independent of effects on plasma lipids but were associated with significant reductions in blood pressure. At any level of lesion severity as judged by gross examination, aortic intimal and medial thickness was considerably less in the rabbits treated with captopril than the control group of rabbits. Interestingly, the plaques of captopril-treated WHHL rabbits demonstrated a pronounced decrease in cellularity and an increase in intimal connective tissue (Figure 5). The captopril action might also be mediated by inhibition occurring in the descending thoracic aorta.

Several potential mechanisms could be responsible for the antiatherosclerotic effect of captopril. The effects on blood pressure would be expected to reduce wall tension and thereby influence medial thickness. A lower blood pressure might also reduce arterial permeability and lipoprotein entry into the artery. Perhaps relevant to these observations are our previously published data indicating that long-term reduction of blood pressure in normotensive rats might inhibit age-related changes in the aorta. Epidemiological data also support the concept that low levels of blood pressure may protect from vascular complications.

The captopril action might also be mediated by inhibiting angiotensin II formation and its effects on cellular proliferation, although studies in cultured SMC have shown that angiotensin II induces cell hypertrophy but not hyperplasia. A recent study has indicated that captopril and the ACE inhibitor cilazapril can reduce the degree of myointimal thickening occurring after balloon-catheter injury of rat carotid artery, consistent with an effect on cell proliferation.

**Other Effects of Experimental Hypertension on the Arterial Wall**

Hypertension can have a variety of other effects on the arterial wall. As examples, we have shown that several forms of experimental hypertension in the rat can induce pronounced reduction in both steady-state mRNA levels and immunoprecipitable protein concentrations of a fatty acid binding protein. Additionally, interesting modulation of steady-state mRNA levels of isoforms of sodium-potassium adenosine triphosphatase (Na⁺,K⁺-ATPase) have also been demonstrated in aortic tissue from hypertensive rats. The possible functional and pathological consequences of these various alterations in gene expression are uncertain.

**Summary and Conclusions**

Dynamic changes occur in the arterial wall in response to long-term blood pressure elevation. In the medial layer (Figure 6), there is a prominent increase in cellular mass, collagen, and elastin. The cellular changes typically involve SMC hypertrophy, which at times is also associated with nuclear polyploidy.

Cell culture studies have indicated that SMC growth can be stimulated by a variety of vasoactive agents including catecholamines and angiotensin II. Extending the cell culture studies to the in vivo situation, we have demonstrated that several growth factors are expressed by arterial cells and that hypertension can increase steady-state levels of mRNA for TGF-β and fibronectins in rat aorta. The fibronectin data are interesting considering their reported role in cell adhesion, growth, motility, and wound healing, and as mediators of TGF-β effects.

The intimal effects of experimental hypertension summarized in Figure 7 have many of the characteristics observed in response to aging or to hypercholesterolemia. Some of these alterations can result from any type of injury to the vessel wall and can sensitize the artery to atherosclerotic plaque formation in the setting of pronounced hyperlipidemia. Whether similar changes also can be affected in the

**FIGURE 6.** Diagram summarizing the effects of hypertension (HBP) on the arterial media. SMC, smooth muscle cell; CT, connective tissue.

**FIGURE 7.** Diagram summarizing the effects of hypertension (HBP) on the arterial intima. SMC, smooth muscle cell; L.P., lipoprotein.
presence of relatively mild hypercholesterolemia of the degree observed in most hypertensive patients is unknown as yet.

Several antihypertensive drugs have been shown to inhibit the development of atherosclerosis in normotensive cholesterol-fed animals, which suggests that blood pressure lowering itself might somehow mediate a protective effect, even within the normal range of blood pressure. Our recent study demonstrating an inhibitory action of captopril on atherogenesis is particularly interesting because of the effectiveness of the drug in the WHHL rabbit model in which other antihypertensive drugs have as yet failed to inhibit the disease. Additionally, captopril appears associated with a reduction in cellularity of atherosclerotic lesions, which suggests that the effect might at least in part involve an action on cellular growth.

The recent advances in cellular and molecular biology, the availability of tissue culture systems for studying vascular cells, and the development of new experimental animal models for studying how changes in blood pressure affect arterial disease in vivo provide excellent opportunities for future research in this field. An improved understanding of how hypertension influences vascular biology should lead to better methods for prevention of coronary atherosclerosis and myocardial infarction.

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Key Words • atherosclerosis • antihypertensive drugs • growth substances • essential hypertension • rabbit studies
1989 Corcoran lecture: adaptive and maladaptive responses of the arterial wall to hypertension.
A V Chobanian

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