Resistance Artery Mechanics, Structure, and Extracellular Components in Spontaneously Hypertensive Rats
Effects of Angiotensin Receptor Antagonism and Converting Enzyme Inhibition

Hope D. Intengan, PhD; Gaétan Thibault, PhD; Jin-Sheng Li, MD, PhD; Ernesto L. Schiffrin, MD, PhD, FRCPC

Background—Altered vascular mechanics resulting from changes in collagen and integrins may influence resistance artery structure and function and, therefore, peripheral resistance and blood pressure in spontaneously hypertensive rats (SHR).

Methods and Results—Effects of age, angiotensin-converting enzyme inhibition (fosinopril, 10 to 30 mg/kg per day), and AT_{1}-receptor antagonism (irbesartan, 50 mg/kg per day) on vascular structure, mechanics, and composition were assessed in SHR. Systolic blood pressure was elevated in young SHR (130 ± 2 mm Hg) compared with Wistar-Kyoto (WKY) rats (106 ± 2 mm Hg). In adult SHR, the rise in systolic blood pressure (44 ± 3 mm Hg) was blunted by fosinopril (18 ± 1 mm Hg) and irbesartan (9 ± 3 mm Hg). Lumen diameter of mesenteric resistance arteries was smaller and media/lumen ratio was greater in young and adult SHR versus WKY rats. Growth index was 24% in untreated adult SHR versus WKY rats; these values were −35% for fosinopril-treated and −29% for irbesartan-treated SHR versus untreated SHR. Isobaric wall stiffness was normal despite increased stiffness of wall components in adult SHR vessels. Irbesartan partially prevented stiffening of wall components in SHR. The collagen/elastin ratio was greater in adult SHR vessels (6.5 ± 1.3) than in WKY (3.2 ± 0.4) vessels. Expression of \(\alpha_\beta_3\) and \(\alpha_\beta_1\) integrins was increased in SHR aged 20 versus 6 weeks. Expression of \(\alpha_\beta_3\) integrins was lower in young SHR, and \(\alpha_\beta_1\) integrins were overexpressed in adult SHR versus WKY rats. Irbesartan and fosinopril attenuated differences in the collagen/elastin ratio and integrin expression.

Conclusions—Wall components of mesenteric resistance arteries stiffen with age in SHR. Interrupting the renin-angiotensin system has normalizing effects on integrin expression and composition, stiffness, and growth of the arterial wall.

Key Words: arteries ■ mechanics ■ remodeling ■ collagen ■ cell adhesion molecules

Resistance arteries of spontaneously hypertensive rats (SHR) undergo a combination of hypertrophic (increased media thickness and cross-sectional area) and eutrophic (decreased lumen and external diameters with unaltered media cross-sectional area) remodeling. Changes in small artery mechanics may also influence pressure-diameter relations of blood vessels. Opposing changes in wall stiffness occur with aging in different arterial beds in hypertensive rats. Increased distensibility of cerebral arterioles from 6- to 8-month-old stroke-prone SHR (SHR-SP) was absent in younger (3- to 4-month-old) SHR-SP, suggesting that prolonged hypertension increases pial arteriole compliance and decreases geometry-independent wall stiffness despite vascular hypertrophy. Decreased vascular stiffness is not a global response to prolonged hypertension. In 2-kidney 1-clip renal hypertensive rats, carotid arteries were stiffer after 9 and 24 weeks, but at 1 and 5 weeks after renal artery clipping, no stiffening had occurred. With chronic exposure to high blood pressure, carotid arteries in this model stiffen,7 whereas in SHR-SP, pial arterioles become less stiff.

Vascular stiffening may involve changes in wall composition. An increased proportion of more distensible (smooth muscle and elastin) to less distensible (collagen and basement membrane) elements may underlie decreased pial arteriolar stiffness in SHR-SP.6 Vascular stiffness may also be modulated by adhesion molecules. Integrins, physical connectors between the extracellular matrix and cytoskeleton, also mediate signal transduction. They are composed of noncovalently linked \(\alpha\) and \(\beta\) subunits, the interaction of which dictates ligand specificity. On the basis of the broad spectrum of integrin functions, vascular remodeling and/or stiffening probably involves changes in these anchorage sites. For example, fibronectin and its receptor, the \(\alpha_\beta_3\) integrin, may modulate aortic stiffness in SHR.8

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We hypothesized that age-related modifications in media components and/or integrins define resistance artery abnormalities in SHR. Specifically, we proposed that with aging in SHR, mesenteric resistance arteries stiffen in association with increased collagen deposition and integrin expression. To study the latter, we used 125I-echistatin, a 49–amino acid peptide found in venom of Echis carinatus, and its ability to bind α,β integrins and possibly other Arg-Gly-Asp (RGD)-binding integrins in a nondissociable manner. We also tested whether antihypertensive treatment with an AT1-angiotensin receptor antagonist (irbesartan) or an angiotensin-converting enzyme inhibitor (fosinopril) would ameliorate hypertension-related differences in artery wall stiffness, media components, and integrin profile.

### Methods

#### Animals

The present study was conducted according to recommendations from the Animal Care Committee of the Clinical Research Institute of Montreal and the Canadian Council of Animal Care. Male SHR and Wistar-Kyoto (WKY) rats were obtained from Taconic Farms (Germantown, NY) and housed under a 12-hour light/dark cycle at 22°C and 60% humidity. Starting at 10 weeks, rats were fed powdered diets (Purina Chow) containing fosinopril (10 mg/kg per day for 4 weeks), irbesartan (50 mg/kg per day), or neither drug until the age of 20 weeks. Irbesartan and fosinopril were provided by Dr James Powell (Bristol-Myers Squibb, Princeton, NJ).

#### Preparation of Small Arteries

Rats were killed at 6 or 20 weeks of age by decapitation, and mesenteric vasculature was isolated. A third-order artery (~2 mm) was placed on 2 glass microcannulas in a pressure myograph and adjusted so that vessel walls were parallel without stretch. Vessels were equilibrated (1 hour) under constant intraluminal pressure (45 mm Hg) with warm (37°C) physiological salt solution (PSS), which was bubbled with 95% air and 5% CO2 to achieve a pH of 7.4. Vessels were unbuckled by adjusting the cannulas. Intraluminal pressure was raised to 140 mm Hg 3 times, and arteries were deactivated by perfusing with Ca²⁺-free PSS containing 10 mmol/L EGTA for 30 minutes. Lumen and media dimensions were measured with the intraluminal pressure maintained at 45 mm Hg.

#### Vascular Morphology

Vessels were deactivated by perfusing with Ca²⁺-free PSS containing 10 mmol/L EGTA for 30 minutes. Lumen and media dimensions were measured with the intraluminal pressure maintained at 45 mm Hg.

#### Vascular Mechanics

Intraluminal pressure was raised to 140 mm Hg 3 times, and arteries were unbuckled by adjusting the cannula. Intraluminal pressure was increased stepwise to 140 mm Hg, and media and lumen dimensions were measured at 5 points. Initial diameter was measured at 3 mm Hg. If the vessel collapsed, lumen diameters at 10 to 140 mm Hg were fit to a third-order polynomial equation, and initial diameter was estimated.

#### Morphological and Mechanical Methods

For definitions of parameters, see Reference 12. Media cross-sectional area is calculated as \((\pi/4) \times (D_e^2 - D_i^2)\), where \(D_e\) and \(D_i\) are external and lumen diameters, respectively. Incremental distensibility is calculated as \((1/\Delta P) \times (\Delta D/\Delta D)\) per change in intraluminal pressure (\(\Delta P\)). Circumferential strain (\(\epsilon\)) is \((D - D_i)/D_o\), where \(D\) is the lumen diameter for a given intraluminal pressure, and \(D_o\) is the original diameter at 3 mm Hg. Circumferential stress (\(\sigma\)) is \((PD)/(2M)\), where \(P\) is the intraluminal pressure (dyne/cm²), and \(D\) and \(M\) are lumen diameter and media thickness, respectively. Elastic modulus was determined by fitting stress-strain data to \(\sigma = \sigma_0 e^{\theta_0}\), where \(\sigma_0\) was

### Table 1: Blood Pressure and Morphology of Relaxed Mesenteric Resistance Arteries From Young (6-Week-Old) SHR and WKY Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WKY (6 wk)</th>
<th>SHR (6 wk)</th>
<th>SHR + Irbesartan</th>
<th>SHR + Fosinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>134±2</td>
<td>95±2</td>
<td>91±2</td>
<td>89±2</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>106±2</td>
<td>130±2†</td>
<td>120±2†</td>
<td>120±2†</td>
</tr>
<tr>
<td>Lumen diameter, μm</td>
<td>229±10</td>
<td>180±9*</td>
<td>170±8</td>
<td>170±8</td>
</tr>
<tr>
<td>External diameter, μm</td>
<td>252±11</td>
<td>203±10*</td>
<td>190±9</td>
<td>190±9</td>
</tr>
<tr>
<td>Media thickness, μm</td>
<td>11.3±0.8</td>
<td>11.7±0.5</td>
<td>11.4±0.6</td>
<td>11.4±0.6</td>
</tr>
<tr>
<td>Media/lumen ratio, %</td>
<td>4.9±0.3</td>
<td>6.5±0.1*</td>
<td>6.4±0.1</td>
<td>6.4±0.1</td>
</tr>
<tr>
<td>Media cross-sectional area, μm²</td>
<td>8637±843 (7254±646)</td>
<td>7098±647</td>
<td>7008±647</td>
<td></td>
</tr>
<tr>
<td>Slope of elastic modulus vs stress</td>
<td>5.6±0.7</td>
<td>6.8±0.7</td>
<td>6.6±0.7</td>
<td>6.6±0.7</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Small artery parameters were measured at an intraluminal pressure of 45 mm Hg. In parentheses, media cross-sectional area has been corrected for greater body weight of WKY rats by multiplying by 0.84=(95/134)². *P<0.01 and †P<0.05 vs WKY rats.

Figure 1. Top, SBP of adult SHR and WKY rats. SHR groups were untreated, treated with irbesartan (50 mg/kg per day), or treated with fosinopril (10 to 30 mg/kg per day). Error bars indicating SEM are hidden by symbols. †P<0.05 vs WKY rats. SHR+irbesartan vs WKY and SHR+fosinopril-treated SHR vs untreated SHR. Bottom, Growth index of mesenteric arteries in SHR showing untreated SHR vs WKY and irbesartan- or fosinopril-treated SHR vs untreated SHR.
TABLE 2. Blood Pressure, Morphology, and Media Composition of Relaxed Mesenteric Resistance Arteries From Adult (20-Week-Old) SHR and WKY Rats: Effects of Irbesartan and Fosinopril

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WKY (20 wk)</th>
<th>SHR (20 wk)</th>
<th>Irbesartan (20 wk)</th>
<th>Fosinopril (20 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (15 wk old), g</td>
<td>367±2</td>
<td>237±6*</td>
<td>233±4*</td>
<td>232±5*</td>
</tr>
<tr>
<td>Body wt (20 wk old), g</td>
<td>564±9</td>
<td>385±6*</td>
<td>355±9*</td>
<td>368±8*</td>
</tr>
<tr>
<td>Heart wt/100 g body wt (20 wk old)</td>
<td>0.310±0.005</td>
<td>0.440±0.009†</td>
<td>0.371±0.007†</td>
<td>0.413±0.006‡</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>113±1</td>
<td>206±2*</td>
<td>168±2‡</td>
<td>186±3‡</td>
</tr>
<tr>
<td>Increase in SBP from 10 to 20 weeks of age, mm Hg</td>
<td>1±2</td>
<td>44±3*</td>
<td>9±3</td>
<td>18±1*‡</td>
</tr>
<tr>
<td>Lumen diameter, μm</td>
<td>249±6</td>
<td>183±7*</td>
<td>174±13*</td>
<td>162±7*</td>
</tr>
<tr>
<td>External diameter, μm</td>
<td>275±7</td>
<td>224±8*</td>
<td>205±14*</td>
<td>192±7*</td>
</tr>
<tr>
<td>Media thickness, μm</td>
<td>12.8±0.9</td>
<td>20.4±1.3*</td>
<td>15.3±1.1†</td>
<td>15.3±0.3§</td>
</tr>
<tr>
<td>Media/lumen ratio, %</td>
<td>5.1±0.3</td>
<td>11.1±0.6*</td>
<td>9.0±0.6§</td>
<td>9.5±0.4*</td>
</tr>
<tr>
<td>Media cross-sectional area, μm²</td>
<td>10 585±938 (8680±769)</td>
<td>13 091±1162</td>
<td>9315±1311</td>
<td>8497±408§</td>
</tr>
<tr>
<td>Slope of elastic modulus vs stress</td>
<td>4.1±0.4</td>
<td>6.9±0.5†</td>
<td>6.7±1.2</td>
<td>7.2±0.5*</td>
</tr>
<tr>
<td>No. smooth muscle cell layers</td>
<td>3.3±0.2</td>
<td>3.8±0.1</td>
<td>3.6±0.2</td>
<td>3.6±0.4</td>
</tr>
<tr>
<td>Smooth muscle cell volume density, %</td>
<td>72.3±2.3</td>
<td>64.4±1.6</td>
<td>66.8±4.6</td>
<td>70.0±2.5</td>
</tr>
<tr>
<td>Collagen volume density, %</td>
<td>20.5±1.9</td>
<td>30.0±1.8*</td>
<td>22.9±1.1§</td>
<td>23.5±1.6§</td>
</tr>
<tr>
<td>Elasticity of vessel, %</td>
<td>7.1±0.8</td>
<td>5.7±0.7</td>
<td>10.3±4.0</td>
<td>6.5±1.1</td>
</tr>
<tr>
<td>Collagen/elastin ratio</td>
<td>3.2±0.4</td>
<td>6.5±1.3†</td>
<td>3.4±0.6§</td>
<td>4.5±0.7</td>
</tr>
</tbody>
</table>

Values are mean±SEM; wt indicates weight. Small artery parameters were measured at an intraluminal pressure of 45 mm Hg. In parentheses, media cross-sectional area has been corrected for the greater body weight of WKY rats by multiplying by 0.82.

*P<0.01 and †P<0.05 vs WKY rats. ‡P<0.01 and §P<0.05 vs untreated SHR.

Determination of Resistance Artery Wall Composition

Deactivated arteries were pressurized at 45 mm Hg and processed for electron microscopy. Electron micrographs (final magnification ×12 000) of 12 to 15 sections per vessel were obtained with a JEM-1200EX electron microscope (JEOL Ltd) and scanned (ScanJet 12000). Cross-sectional areas of normotensive vessels. Growth index is calculated as the external diameter of hypertensive vessels and CSAe is the cross-sectional area of normotensive vessels. Growth index is calculated as (CSAt-CSAr)/(CSAr)×100. Values are mean±SEM. Data are presented as mean±SEM. Unpaired Student t test (young rats) and 1-way ANOVA followed by a Student-Newman-Keuls test (adult rats) (or Mann-Whitney test and Kruskal-Wallis tests, respectively, where standard deviations were different) and ANOVA for repeated measures were used as appropriate. Interaction means were analyzed for “simple main effects” by Student t test for unpaired data (young rats) and Student-Newman-Keuls (adult rats) test. A value of P<0.05 was considered significant.

Results

Body Weight, Blood Pressure, and Small Artery Morphology

Body weights were lower in SHR than in age-matched WKY rats, whereas in adult SHR, SBP was significantly higher than in age-matched WKY rats (Figure 1). Between 10 and 20 weeks of age, SBP rose significantly in untreated SHR but to a lesser degree (P<0.01) in SHR treated with irbesartan and fosinopril (Figure 1 and Table 2).

Lumen and external diameters were smaller (Figure 2), media/lumen ratio was greater, and media cross-sectional

stress at D0 and D1 is a constant related to the rate of increase of the stress-strain curve. Tangential elastic modulus (ET) was calculated at several values of stress from the derivative of the aforementioned exponential curve: ET=∂σ/∂ε=ε(p−ε)6. Remodeling index is calculated as 100×[(D0ε−D0)/((D0)/2(ε−D0ε)), where (D0)ε and (D0) are lumen diameters of normotensive and hypertensive vessels, respectively, and (D0ε) is the external diameter of hypertensive vessels and CSAe is the cross-sectional area of normotensive vessels. Growth index is calculated as (CSAr−CSAs)/CSAr, where CSAe and CSAe are media cross-sectional areas of normotensive and hypertensive vessels, respectively.

Identification of RGD-Binding Integrins

After electrophoresis, [125I]-echistatin complexes were transferred to a nylon membrane, which was immediately subjected to autoradiography for band localization. The membrane was blocked (0.5% Tween, 10% goat serum, 1% polyvinylpyrrolidone, and 2.5% to 5% milk), washed, and incubated with mouse anti-human integrin αv (1:500, Chemicon International Inc), mouse anti-rat integrin β1 (1:1000, Pharmingen Canada), rabbit anti-human integrin α1 (1:2500, Chemicon International Inc), or hamster anti-rat integrin β1 (1:200, Pharmingen Canada). Membranes were washed in PBS and treated with the appropriate secondary antibody. Goat anti-mouse (1:10 000) and anti-rabbit (1:20 000) antibodies were conjugated with horseradish peroxidase. Membranes treated with goat anti-hamster antibody (1:1000) were exposed to streptavidin peroxidase conjugate (1:1000) for 30 minutes. Signals were detected by chemiluminescence.
Figure 2. Lumen diameter–intraluminal pressure (top panels), external diameter–intraluminal pressure (middle panels), and media cross-sectional area–intraluminal pressure (bottom panels) curves in relaxed mesenteric arteries from 6-week-old (left) and 20-week-old (right) SHR and WKY rats (n=6). Error bars indicate SEM. *P<0.05 vs age-matched WKY rats. †P<0.05 vs age-matched, untreated SHR.
Figure 3. Incremental distensibility–intraluminal pressure (top panels), media stress–intraluminal pressure (middle panels), and media stress–strain (bottom panels) curves in relaxed mesenteric arteries from 6-week-old (left) and 20-week-old (right) SHR and WKY rats (n=6). Error bars indicate SEM. *P<0.05 and **P<0.01 vs age-matched WKY rats.
area was similar in vessels from SHR versus age-matched WKY rats (Table 2). In adult but not young SHR, media width was greater in SHR than in WKY vessels. Irbesartan reduced media width and media/lumen ratio, and fosinopril reduced media width and media cross-sectional area in adult SHR vessels (Tables 1 and 2).

In adult SHR, remodeling and growth indices were 88% and 24%, respectively (Figure 1), measured at an intraluminal pressure of 45 mm Hg. These represent percentages of the difference in lumen diameter between hypertensive and normotensive vessels that are attributable to eutrophic remodeling and to growth. Irbesartan and fosinopril produced hypotrophy resulting in growth indices of 29% and 35%, respectively, relative to untreated SHR vessels.

Vascular Mechanics
Increasing intraluminal pressure to 140 mm Hg decreased the media/lumen ratio of relaxed vessels from young and adult SHR and WKY rats to similar degrees (data not shown) without altering media cross-sectional area, since the media is incompressible (Figure 2). Lumen and external diameters expanded less with increasing pressure in SHR versus WKY rats (Figure 2), indicating reduced capacity for passive dilation in mesenteric arteries from SHR irrespective of age. Distensibility was normal at physiological pressures (40 to 140 mm Hg, Figure 3) in SHR arteries, suggesting that when collagen has been recruited, distensibility is so low that media thickening does not lower it further.

Increasing intraluminal pressure increased media stress more in WKY than in SHR arteries (P<0.05), regardless of age (Figure 3). The stress-strain curve was shifted leftward in mesenteric arteries from SHR compared with those from age-matched WKY rats (Figure 3).

When plotted against intraluminal pressure or stress, incremental elastic modulus (wall stiffness) was similar between young WKY and SHR arteries (Figure 4, Table 1). In adult SHR, however, the slope of the incremental elastic modulus versus stress was augmented (Figure 4, Table 2). Pressure is transduced to the vessel wall as stress differentially depending on vessel geometry; thus, the relation between elastic
Vascular remodeling in hypertension involves 2 processes. In eutrophic remodeling, wall material appears rearranged around a reduced lumen without evidence of net growth. In hypertrophic remodeling, the media cross section is increased and encroaches on the lumen, indicating the presence of growth. As indicated by the growth index of 24%, vascular growth occurred in untreated 20-week-old SHR. The remodeling index of 88% may indicate eutrophic remodeling but is probably partially due to mechanical alterations, since wall components were stiffer in adult SHR.

The interplay between structure and mechanics of resistance arteries from adult SHR is complicated. The thickened media, by lowering wall stress induced by high pressure, counters late-stage rigidity of wall components so that isobaric stiffness (resulting from wall components and vessel geometry) is not reduced in SHR. This is consistent with previous results obtained also in mesenteric resistance and carotid arteries. At 20 weeks of age, despite significant stiffening of wall components, geometric adaptation has occurred in SHR to maintain normal in vivo wall stress and stiffness, protecting the vessel wall from pressure-induced damage. In our initial report, isotropic stiffness of mesenteric arteries was also normal in adult SHR, but in that study, stiffness of wall components was lower, perhaps because of differences between groups of SHR. The important common finding is strict regulation of isobaric arterial stiffness in SHR, whether by modulating geometry or stiffness of wall components.

Stiffening of wall components in SHR agrees with our recent finding that collagen/elastin ratios are increased in 20-week-old SHR mesenteric small arteries versus WKY arteries, also confirmed here. Just as increases in elastin may have diminished stiffness of SHR-SP pial arterioles, increased collagen and, therefore, collagen recruitment at lower strain may increase stiffness of SHR mesenteric small arteries. Modifying media composition is not the sole mechanism involved in resistance artery stiffening in SHR. Irbesartan and fosinopril normalized the collagen/elastin ratio in SHR arteries, but only irbesartan reduced arterial stiffness. Also, in human subcutaneous resistance arteries, despite increased collagen/elastin ratios, wall stiffness was lower in vessels from mildly hypertensive patients.

Changes in RGD-binding integrins that mediate adhesion of cells to the extracellular matrix may contribute to arterial remodeling and stiffness of the vascular wall. Integrins are abnormal in SHR, with a decrease in $\alpha_\beta_1$ integrins in young SHR arteries and an increase in $\alpha_\beta_1$ integrins in adult SHR. Increasing cell-matrix attachment sites, perhaps via fibronectin and $\alpha_\beta_3$ integrins, may participate in mechanical adaptation of aortas in SHR, where connections between smooth muscle cells and elastic lamellas are numerous. $\alpha_\beta_3$ and $\alpha_\beta_1$ integrins increased significantly in mesenteric arteries of SHR from 6 to 20 weeks of age. This may represent an increase in cell-matrix attachment sites intended to modulate arterial structure and mechanics in hypertension. However, as with collagen, irbesartan and fosinopril corrected integrin abnormalities in adult SHR arteries, but only irbesartan reduced arterial stiffness. Thus, neither wall composition nor integrin profile is the sole determinant of arterial stiffness. Perhaps topographical distribution (clustering?) of integrin-mediated attachment sites between ex-
tracellular matrix and vascular smooth muscle cells determines vascular stiffness in hypertension.

Likewise, expression levels of integrins are not sole determinants of eutrophic remodeling. Normalization of integrins by irbesartan and fosinopril was not paralleled by regression of remodeling, again suggesting that topographical distribution of attachment sites may be important. However, altered integrin status may be related to the growth component, because both irbesartan and fosinopril produced hypotrophic remodeling. Aside from acting as a physical joint, \( \alpha_\beta_3 \) integrins may promote growth functionally. Interactions between \( \alpha_\beta_3 \) integrins and tenascin-C (an extracellular matrix glycoprotein that is prominent in remodeling tissues) promote epidermal growth factor–dependent growth and survival of rat pulmonary artery smooth muscle cells.22 Because tenascin-C induction was also accelerated in SHR aortas,23

Figure 6. a. Expression of \( \alpha_\beta_1 \) and \( \alpha_\beta_3 \) integrins in mesenteric arteries from young SHR vs age-matched WKY rats (n=6). * \( P < 0.05 \). b. Expression of \( \alpha_\beta_3 \) and \( \alpha_\beta_1 \) integrins in adult SHR mesenteric arteries. ** \( P < 0.01 \) vs age-matched WKY arteries. † \( P < 0.01 \) vs untreated SHR arteries. c. Difference in percentage between SHR (6 and 20 weeks old) and age-matched WKY rats. IRBE indicates irbesartan; and FOS, fosinopril. * \( P < 0.05 \) vs 6-week-old SHR. † \( P < 0.05 \) vs untreated 20-week-old SHR (n=6). Error bars indicate SEM.
tenasin-C and/or other α,β, integrin ligands may protect smooth muscle cells from apoptosis and promote proliferation and subsequent extracellular matrix deposition.

Vascular remodeling is preventable by early treatment with angiotensin-converting enzyme inhibitors 24–27 and AT1-receptor antagonists. 27,28 Losartan also improved vascular structure when administered late to SHR. 29 In the present study, with mild blood pressure reduction (from 26 to 35 mm Hg), interrupting the renin-angiotensin system with irbesartan and fosinopril blunted small artery growth with growth indices of −29% and −35%, respectively, relative to untreated SHR. There was little effect on eutrophic remodeling.

Neither irbesartan nor fosinopril normalized blood pressure or remodeling completely. Vascular remodeling in SHR lowered wall stress (Figure 3), protecting the vessel from residually elevated blood pressure. If, in addition to preventing growth, irbesartan and fosinopril had reversed remodeling, high pressures would have increased wall stress significantly, predisposing the vascular wall to further damage. The remodeled lumen reduced circumferential wall tension and media stress, thereby acting protectively in the face of persistently high blood pressure after correction of the growth component.

In conclusion, SHR exhibit eutrophic remodeling of mesenteric resistance arteries by 6 weeks of age, and by 20 weeks, a combination of vascular growth and remodeling is seen. Interrupting the renin-angiotensin system interfered with growth but not eutrophic remodeling of resistance arteries in 20-week-old SHR. Whereas arterial stiffness was normal in young SHR, with aging to 20 weeks, components of the arterial wall became stiffer. In adult SHR, differences in lumen diameter may result from a combination of increased stiffness and eutrophic remodeling. A critical finding here is that the arterial wall adapts geometrically to tightly maintained physiologically relevant pressure-buffering capacity (ie, distensibility and isobaric stiffness) despite the presence of stiff components in the vessel wall. AT1-receptor blockade improved resistance artery wall stiffness. An increase in the proportion of less distensible (collagen) to more distensible (elastin) components in adult SHR, accompanied by an age-related increase in α,β, and α,β, integrins, may contribute to remodeling and stiffening of resistance arteries in this genetic model of hypertension.

Acknowledgments

This study was supported by grants from the Medical Research Council of Canada to the Multidisciplinary Research Group on Hypertension, from the Fondation des Maladies du Coeur du Quebec, and from Bristol-Myers Squibb (Princeton, NJ). Dr Intengan is supported by a fellowship from the Medical Research Council of Canada. The authors are grateful to Andre Turguen and Genevieve Lapalme for technical assistance.

References


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Circulation. 1999;100:2267-2275
doi: 10.1161/01.CIR.100.22.2267

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