Ventricular/Vascular Coupling and Regional Arterial Dynamics in the Chronically Hypertensive Baboon: Correlation With Cardiovascular Structural Adaptation


Ventricular/vascular coupling dynamics and regional hemodynamics of five hypertensive baboons with concentric left ventricular (LV) hypertrophy (mean arterial pressure ±SD, 148 ± 16 mm Hg; LV mass/body weight ratio 3.42 ±0.8) were compared with five normotensive controls (mean arterial pressure 89 ±3 mm Hg; LV mass/body wt ratio 2.73 ±0.5) at different mean arterial pressures. Ventricular/vascular dynamics were assessed by aortic input impedance, pulsatile/total power ratio, effective arterial elastance and compliance from a three-element Windkessel "lumped" model of the circulation. Regional arterial dynamics were assessed by pulse-wave velocities and local reflection coefficients. Systemic arterial compliance was similarly decreased with elevated pressure in both groups but was significantly more reduced for the hypertensive group compared with control animals at control (0.49 ±0.16 vs. 0.96 ± 0.09 ml/mm Hg; p<0.05) and acutely lowered arterial pressure (0.62 ±0.26 vs. 1.41 ± 0.24 ml/mm Hg, respectively). Changes in compliance were paralleled by differences in effective arterial elastance derived from cinerventriculographic pressure-volume ratios. Regional foot-foot and apparent phase pulse-wave velocities were significantly increased for distal aortic segments of the hypertensive animals during elevated pressures compared with controls (q,, 17.5 ±7.5 vs. 8.7 ± 3.0 m/sec; p<0.05). Histology of the aorta revealed significant increases in collagen content (µg/mg dry wt) from proximal to distal aortic segments (27 ± 2.5 vs. 38 ±6; p<0.005) in hypertensive animals but not in controls (27 ±2 vs. 32 ±6; NS). With pharmacological normalization of systemic arterial pressures, hypertensive baboons developed aortic wave speeds similar to controls but manifested significantly reduced compliance compared with controls. In contrast, with acute elevations of pressure, systemic arterial aortic compliances were similar for both groups, but distal pulse-wave velocities were significantly increased for hypertensive animals compared with controls. We conclude that measures of ventricular/vascular coupling and arterial dynamics are determined by both the level of arterial pressure and the physical characteristics of the cardiovascular system in chronic systemic hypertension and pressure overload ventricular hypertrophy. (Circulation Research 1988;63:798–811)

There has been a longstanding interest in the pathophysiology of systemic hypertension. The early emphasis on etiologic factors included consideration of the resistive load as a primary causative mechanism.1,2 Subsequent emphasis centered on the possible contribution of changes in the capacitive load3,4 or changes in vasomotor tone5 to the cardiovascular consequences of hypertension. More recent investigations have focused on the ventricular/vascular interaction to suggest
that mechanisms in addition to mean systemic pressure and peripheral resistance contribute to the total cardiac hydraulic load.4,6

Limitations of previous work include animal models in which hypertension is most often acute (pharmacological) or of short duration. In addition, there is marked regional variation in vascular histology, the significance of which is unknown.7-9 Furthermore, alterations of this morphometric pattern with chronic hypertension may not be uniform throughout the arterial tree.10 Some animal data suggest that central aortic compliance does not play a significant role in hypertension4; however, a decrease in total systemic compliance has been demonstrated in hypertensive man compared with controls at similar arterial pressures.11 Arterial compliance changes are usually considered as secondary to longstanding mechanical stress on the entire vascular tree and are often used to discriminate hypertensive populations by means of noninvasive Doppler-derived pulse-wave velocities.12 Results of clinical investigations are difficult to interpret because of the variable and unknown duration of hypertension in subjects studied and the confounding effects of age and atherosclerosis on ventricular function and arterial dynamics in hypertensive subjects.

Another shortcoming in this field of study is that terminology associated with "ventricular/vascular coupling" or "interaction" has been ill-defined. The phrase "ventricular/vascular coupling" is not a specific number or index but a variety of analytical approaches that attempt to quantitate the interaction between the ventricle and systemic circulation. Ventricular/vascular coupling may be assessed in a number of ways, such as by the traditional calculation of aortic input impedance or pulsatile/total power ratio. More recently, effective arterial elastance from the end-systolic pressure/stroke volume ratio or application of a three-element Windkessel "lumped" model of circulation to determine characteristic impedance, compliance, and resistance have been used to express the pressure response to a given flow or stroke volume from the ejecting ventricle.

We conducted the present investigation in an animal phylogenetically close to man with chronic renal hypertension of known duration to 1) examine the differences, if any, in ventricular/vascular coupling and regional arterial dynamics between normal baboons and baboons with longstanding experimental renal hypertension as a function of acutely altered mean aortic pressure, 2) examine the regional morphometric structural properties of the aortic wall as a possible basis for differences in regional arterial dynamics in hypertensive study animals compared with normotensive controls, and 3) to evaluate whether ventricular/vascular coupling assessed under these in vivo conditions using an effective arterial elastance derived from ventricular end-systolic pressure-volume relations would compare favorably with compliance derived from the more conventional three-element Windkessel model of circulation. Regional hemodynamics were described in terms of pulse wave velocities and local reflection coefficients.

Materials and Methods

The study population consisted of five mature baboons with secondary hypertension (Group 2) and five normotensive, age-sex matched controls (Group 1). Hypertension was surgically induced by unilateral renal artery clip or bilateral kidney wrap resulting in a 66% elevation in mean arterial pressure for 3½ years prior to study.13 The control normotensive group consisted of animals which received a similar operation but failed to develop arterial hypertension. Part of the arterial hemodynamics at normotensive pressures in these control baboons was previously reported from this laboratory.15

Procedure

After premedication with ketamine (20 mg/kg i.m.) the baboons were intubated and studied under 0.8% halothane anesthesia. Autonomic blockade was produced by premedication with intravenous propranolol (0.15 mg/kg) and atropine (0.06 mg/kg) to attenuate β-adrenergic and cholinergic reflexes secondary to pharmacological load alterations. Both carotid arteries and a femoral artery at the inguinal ligament were surgically exposed and isolated. A multisensor catheter with six pressure transducers mounted at 10 cm intervals14,15 was introduced through an arteriotomy in the right femoral artery and advanced to position the tip in the aortic root. Another multisensor catheter with two pressure transducers (one at the distal tip and one 4 cm proximal) and an electromagnetic flow velocity probe mounted with the proximal pressure transducer housing was introduced via the right carotid artery and positioned with the tip in the left ventricle and proximal sensor in the aortic root just distal to the aortic valve. Simultaneous pressures from the left ventricle, aortic root, proximal descending, lower thoracic, abdominal aorta, and iliac artery were measured in addition to simultaneous aortic input flow. A balloon-tipped, flow-directed thermodilution catheter was introduced via the right internal jugular vein and positioned in the pulmonary artery with fluoroscopic guidance.

Pressure signals were processed with Honeywell Accudata 143 general purpose preamplifiers filtered with a low pass filter (corner frequency 100 Hz; Waltham, Massachusetts). Each pressure transducer was dynamically calibrated to a mercury standard prior to catheter insertion. Flow signals were processed using a Biotronex 613-2E dual-channel flowmeter (Kensington, Massachusetts) and were filtered at 100 Hz. The flowmeter has a linear phase shift with frequency corresponding to an intrinsic processing delay of 5 msec. Velocity signals were calibrated to flow in milliliters per second by simultaneous thermodilution cardiac outputs.
A 7F angiographic catheter with a single high fidelity micromanometer (Millar Instruments, Houston, Texas) at the tip was introduced via the left carotid into the aortic root. This catheter was used for contrast injections to obtain ventriculograms and aortography. Baseline pressures and ascending aortic flow were measured and recorded on FM analog tape (Honeywell 5600C recorder). Biplane left ventriculography and full length aortography at 60 frames/sec were obtained after baseline hemodynamics were recorded.

Angiographic Technique

Biplane contrast cineventriculography (CGR Arcomax, Baltimore, Maryland) was performed at 60 frames/sec in the anteroposterior projection using 20–30 ml of iodinated contrast (Renografin-76) over three seconds at 300 psi. Simultaneous high fidelity left ventricular pressures and biplane angiographic volumes were acquired at control and during both pharmacological interventions. At least 20 minutes elapsed between ventriculograms to permit the effects of iodinated contrast to dissipate. Electrocardiograms and ventricular pressures were recorded at 250 mm/sec paper speed using a Gould Brush 8-channel oscillograph (Houston, Texas). Synchronization between cineangiographic volume and pressure data was accomplished by a cinepulse generator and displayed on the analog pressure recording. Frame-by-frame left ventricular cineangiographic volumes and dimensions were traced using a sonic digitizer (resolution 0.1 mm; Science Accessories, Southport, Connecticut) attached to a cine film projector equipped with an automated frame counter (Vanguard Instruments, Neptune, New Jersey) and interfaced to an IBM PC-XT microprocessor. Biplane left ventricular volumes were determined using a modification of Simpson’s rule algorithm, regression equations validated by left ventricular postmortem cast, and software developed at University of Texas Health Sciences Center in San Antonio.16 Correction for magnification and pin-
Ventricular/Vascular Coupling in Hypertension

Figure 2. The reciprocal of effective arterial elastance (1/Ea) as a function of mean aortic pressure. Upper curve represents the normotensive animals (Group 1); lower curve represents the hypertensive animals (Group 2).

Cushion distortion was performed by filming calibrated grids at the mid-chest position in the antero-posterior and lateral planes. In comparisons of ventricles and altered chamber geometry, wall stress is a more accurate measure of force than pressure since it normalizes for differences in chamber size and wall thickness. Since direct angiographic measurements of left ventricular wall thickness during ejection are subject to considerable errors because of the inclusion of trabeculae and papillary muscles, wall thickness was derived indirectly at 16.6 msec intervals by computer program using the method of Hugenholtz. The methods assume an ellipsoidal of revolution model and a constant left ventricular mass using end-diastolic wall thickness measured from the ventriculogram.

End-systolic stress-volume relations were constructed for each animal using multiple loading conditions. End-systole was defined as the stress-volume relation coincident with the maximal ratio of pressure to volume. This measure of end systole correlates closely with maximal systole elastance determined using sequential isochronal pressure-volume plots in our laboratory. Hemodynamic measurements including angiography were repeated as above in both control and chronically hypertensive baboons during a hypotensive steady state (mean pressure 44 ± 4 mm Hg) induced by nitroprusside infusion (mean dose 2.6 ± 0.5 μg/kg/min, Group 1; 3.1 ± 0.5 μg/kg/min, Group 2) and similarly during a hypertensive steady state (mean pressure 133 ± 6 mm Hg) induced by phenylephrine infusion (7.1 ± 2.2 mg/kg/min, Group 1; 5.1 ± 3.7 mg/kg/min, Group 2). Control pressures under halothane anesthesia were similar for both groups (mean 80 ± 9 mm Hg, Group 1; 76 ± 7 mm Hg).

High fidelity analog left ventricular pressure signals were digitized using an inductance digitizing surface (resolution 0.002 mm, Calcomp) at 5 msec intervals and matched with coincident values for left ventricular cineangiographic wall thickness and chamber geometry by a software based interpolation procedure developed in our laboratory. With these data, we calculated mid-wall circumferential stress for a thick-walled ellipsoid of revolution by the formula of Mirsky:

$$\sigma_c = \frac{(Pb/h)}{\left[1 - \frac{h}{2b} - \frac{b^2}{2a^2}\right]}$$

where P is left ventricular pressure, h is wall thickness, and a and b are the mid-wall semi-major and semi-minor axes, respectively.

Figure 3. Three-element Windkessel model of the systemic circulation and output of the parameter-fitting algorithm. Zc, characteristic impedance; R, peripheral vascular resistance; and C, compliance.
TABLE 1. Population Characteristics

<table>
<thead>
<tr>
<th>Baboon Group</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>LV mass (g)</th>
<th>LV mass/Body wt</th>
<th>Mean Ao Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13 ± 0.7</td>
<td>25.7 ± 7</td>
<td>61.7 ± 26</td>
<td>2.73 ± 0.5</td>
<td>89 ± 3</td>
</tr>
<tr>
<td>2</td>
<td>13 ± 0.7</td>
<td>22.1 ± 5</td>
<td>72.6 ± 32</td>
<td>3.42 ± 0.8</td>
<td>148 ± 16</td>
</tr>
<tr>
<td>p value</td>
<td>0.1</td>
<td>0.17</td>
<td>0.01</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

Group 1, normotensive controls; Group 2, hypertensive animals; LV, left ventricular; Ao, aortic pressure (mean) in the tethered state (under ketamine).

Hg, Group 2). Although end systole has been variably defined,20 we employed the maximum ratio of pressure to volume as previously reported.19 The animals were killed, and the aorta with terminal branches excised. The specimens were examined histologically for wall thickness, presence of atherosclerosis, elastic lamellae, and collagen content.

**Histological Technique**

The aortas, fixed without pressure infusion, were sampled for light microscopy at the level of the most proximal portion of the ascending aorta along the greater curvature, just distal to the left subclavian artery along the greater curvature, just proximal to the coeliac artery on the ventral aspect, and just distal to the inferior mesenteric artery on the ventral aspect of the aorta. The transverse internal aortic diameter at these four levels was measured with a micrometer. Segments of aorta were processed for light microscopy by standard techniques using graded alcohol and xylene, embedded in paraffin and sectioned at 4 μm. An ocular micrometer was used to measure the wall thickness and the number of elastic lamellae seen in Verhoeff’s elastin stains of sections 4 μm thick from each of the four sampled areas of the aorta. Semiquantitatively histological grading of the thickness of elastic lamellae was performed at a magnification of 150. Elastic lamellae were taken to be of normal thickness or mild or moderately increased in thickness dependent upon the increased intensity of elastic staining. Also, the presence of smooth muscle cells was assessed. Areas adjacent to the samples for histological examination was taken for hydroxyproline assays.21

**Data Analysis**

Analog data were converted to digital format using a PDP 11/34 computer. Hard copy of signals was obtained using a fiberoptic strip chart recorder (Honeywell Visicorder Model 1958). Regional foot-foot pulse-wave velocity and apparent phase velocity (using Fourier analysis) between adjacent sites of simultaneous pressure measurement were determined using previously described methods.14

$$c_{app}(n) = \frac{2\pi fn \times \Delta Z}{\Delta \Phi n}$$

(2)

where f is fundamental frequency; n is harmonic number; ΔZ is distance between pressure sensors; and Φn is phase shift for nth harmonic. Mean apparent phase velocity ($c_{app}$) is taken as the average of phase velocities greater than 3 Hz. In the presence of

**TABLE 2. Hemodynamic Characteristics of the Hypertensive Study Group (2) and Normotensive Control Baboons (1)**

<table>
<thead>
<tr>
<th>Pressure range</th>
<th>Low</th>
<th>Control</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>I</td>
<td>II</td>
<td>I</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>725 ± 73</td>
<td>941 ± 229</td>
<td>744 ± 72</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9 ± 5</td>
<td>7 ± 6</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>EDV (cc)</td>
<td>37 ± 20</td>
<td>23 ± 3</td>
<td>38 ± 14</td>
</tr>
<tr>
<td>SV (cc)</td>
<td>31 ± 15</td>
<td>12 ± 3*</td>
<td>21 ± 7</td>
</tr>
<tr>
<td>Zs (d x s x cm$^{-2}$)</td>
<td>124 ± 23</td>
<td>118 ± 25</td>
<td>110 ± 15</td>
</tr>
<tr>
<td>SVR (d x s x cm$^{-2}$)</td>
<td>1,448 ± 64</td>
<td>1,864 ± 282</td>
<td>3,387 ± 605</td>
</tr>
<tr>
<td>ESS (dyne/cm²)</td>
<td>51 ± 7</td>
<td>39 ± 5</td>
<td>126 ± 15</td>
</tr>
<tr>
<td>Ao$_{car}$ (mm Hg)</td>
<td>61 ± 5</td>
<td>77 ± 4</td>
<td>100 ± 8</td>
</tr>
<tr>
<td>Ao (mm Hg)</td>
<td>35 ± 4</td>
<td>36 ± 5</td>
<td>70 ± 10</td>
</tr>
<tr>
<td>Wt</td>
<td>219 ± 103</td>
<td>178 ± 63</td>
<td>361 ± 109</td>
</tr>
<tr>
<td>Wp</td>
<td>35 ± 9</td>
<td>39 ± 19</td>
<td>18 ± 3</td>
</tr>
</tbody>
</table>

Ao$_{car}$, Ao, aortic systolic and diastolic pressures, respectively; dP/dt, peak positive first derivative of left ventricular (LV) pressure; EDV, end-diastolic volume; ESS, end-systolic stress; HR, heart rate; LVEDP, LV end-diastolic pressure; SV, stroke volume; SVR, systemic vascular resistance; Wt, total pulsatile power (mean); Wp, pulsatile power (mean); Zs, characteristic aortic input impedance. *p<0.05 ± SD.
strong local reflections, the lower frequency components of $c_{app}$ are significantly increased and must be considered in the interpretation of mean $c_{app}$.

Foot-foot wave speeds were determined as previously described\textsuperscript{14,15} tangents to the end-diastolic and initial upstroke wave contour between adjacent transducers. The transmission time was determined between intersecting lines and precise distances between transducers were known.

Local reflection coefficients ($\Gamma_i$) were estimated from the relation

$$\Gamma_i = \frac{1 - Z_p / Z_d}{1 + Z_p / Z_d}$$

$Z_{p,d}$ is characteristic impedance of the parent (p) or distal (d) vessels respectively. The pulse-wave velocity ($c$) is related to characteristic impedance ($Z_c$) by

$$Z_c = \frac{c \rho}{A}$$

$Z_c$ is taken to be a real number, which is a limitation for using this derivation but is approximately correct for large arteries where $\rho$ is blood density and $A$ is cross-sectional luminal area. Thus, $\Gamma$ may be calculated for symmetrical bifurcations:

$$\Gamma = \frac{1 - (2A_c c_p / A_c c_d)}{1 + (2A_c c_p / A_c c_d)}$$

and a trifurcation with two equal distal (d) vessels and a third vessel ($A_1$, $c_1$):

$$\Gamma = \frac{1 + \left[ \frac{c_p}{A_p} \left( \frac{A_1}{c_1} + \frac{2A_d}{c_d} \right) \right]}{1 + \left[ \frac{c_p}{A_p} \left( \frac{A_1}{c_1} + \frac{2A_d}{c_d} \right) \right]}$$

Equation 5 is used to calculate $\Gamma$ at the abdominal/iliac junction, and Equation 6 is used at the branch point of the renal arteries.

Figure 4. Example of pressure waveforms in the aorta from the aortic root to the iliac artery for normotensive animals and hypertensive animals. Examples are shown for control and low pressures. The pressures have been artificially offset from one another to allow comparison of wave contours. A calibration scale (100 mm Hg) for pulse pressure is shown.
Fourier analysis was applied to simultaneous aortic input pressure and flow and their respective harmonic components to determine aortic input impedance. Moduli greater than 3 Hz were averaged to determine the characteristic impedance. Fourier data of pressure and flow were also used to calculate pulsatile power \( W_p \), total power \( W_t \), and the \( W_p/W_t \) ratio:

\[
W_m = P_m \times Q_m \\
W_p = \frac{1}{2} \sum P_n \times Q_n \times \cos \Phi_n \\
W_t = W_p + W_m
\]

where \( P_m \) is mean pressure; \( P_n \) is modulus of pressure for the \( n \)th harmonic; \( Q_n \) is flow for the \( n \)th harmonic; \( Q_m \) is mean flow; \( Q_n \) is pulsatile power; \( \Phi_n \) is phase angle of impedance for the \( n \)th harmonic; and \( W_t \) is total power. The kinetic energy components are small and were neglected for determination of total power.

Simultaneous left ventricular pressure and angiographic volume data were used to relate end-systolic pressure and volume to end-systolic pressure at the three mean pressure levels studied were fitted by linear regression and the slope used to estimate ventricular elastance. Using the volume intercept as end-diastolic volume from angiogram, slopes of the end-diastolic volume to end-systolic pressure at each pressure level (see Figures 1A and 1B) were used to estimate effective arterial elastance. The reciprocal of arterial elastance (proportional to and in units of arterial compliance) was plotted as a function of mean pressure (see Figure 2).

A three-element Windkessel model (see Figure 3) was used to determine systemic compliance. Simultaneous pressure and flow input signals were applied to a computer model fitting algorithm to determine parameters of peripheral resistance, characteristic impedance, and compliance. The computer convergence resulted in an estimated flow, which was compared for best fit by \( \chi^2 \)-square to the measured flow (see Figure 3).
FIGURE 6. Demonstrates aortic input impedance in normotensive and hypertensive baboons at low, control and high pressures. Top panel: Average values for normotensive baboons. Bottom panel: Average values for hypertensive baboons.
FIGURE 7. Plot of systemic compliance as a function of mean aortic pressure. Superior curve (*) represents the normotensive group, and the lower curve (+) represents the hypertensive animals. *p<0.05.

Statistics
Parametric variables between pressure levels within groups were compared by the Student's paired t test. Hemodynamic parameters between normotensive and hypertensive subsets at the same pressure level were compared by the unpaired Student's t test. A level of p<0.05 was considered statistically significant. Model estimates of flow were compared for goodness of fit by χ-square to the measured flow. Only correlations with r>0.90 were accepted.

Results
The population characteristics are given in Table 1. The normotensive and hypertensive groups each consisted of three females and two males. Mean arterial pressure was elevated by 66% (p<0.05) in the hypertensive baboons compared with controls. This chronic elevation was associated with a 25% (p<0.05) increase in left ventricular mass/body wt ratio. Hemodynamic characteristics at baseline and study pressures are given in Table 2.

Left ventricular performance revealed similar peak positive dP/dt at low and control pressures for normotensive and hypertensive groups but was greater in hypertensive animals at elevated pressures (1,006±110 vs. 1,349±167 mm Hg • s⁻¹, p<0.05). End-systolic circumferential wall stress (Equation 1) was similar at all pressures for both groups. Left ventricular end-diastolic pressures were similar for both groups at all pressures, but end-diastolic volumes were significantly reduced for Group 2 compared with Group 1 at control (24±3 vs. 38±14 ml; p=0.02) and elevated mean arterial pressure (27±8 vs. 43±16 ml; p=0.04) but not statistically different at low mean pressure. Stroke volumes were similar for both groups at elevated pressures but significantly less in the hypertensive group at low (12±3 vs. 31±7 ml; p=0.04) and control pressures (13±3 vs. 21±7 ml; p=0.02). Finally, the left ventricular elastance determined from the slopes of the end-systolic pressure-volume relations was similar for both groups (see Figures 1A and 1B).

Pressure and flow contours of the hypertensive animals were similar to those of the normotensive animals at low pressure levels. At control pressures, the pulse amplitude tended to be increased for the hypertensive animals (see Figure 4). The diastolic decay of pressure waveforms in distal aortic segments of the hypertensive subset were more oscillatory than controls (see Figure 5) at elevated mean aortic pressures.

Values for pulse-wave velocities are given in Table 3. Velocities were similar in hypertensive and control groups at low and control pressures. During the hypertensive steady state, distal c_app and c_tr were

| Table 3. Pulse-Wave Velocities Along the Aorta and Its Terminal Iliac Branches |
|---------------------------------|-------------------|-------------------|-------------------|-------------------|
|                                | Low              | Control           | High              |
|                                | I    | II   | I    | II   | I    | II   |
| Arch                           |      |      |      |      |      |      |
| c_app                          | 3.7±0.7| 4.6±0.8| 4.8±0.8| 4.2±1.0| 5.3±3.0| 8.5±3.4 |
| c_tr                           | 4.0±0.7| 3.1±0.3| 3.5±0.5| 3.5±1.0| 4.6±0.4| 5.5±0.9 |
| Thor                           |      |      |      |      |      |      |
| c_app                          | 4.7±1.2| 5.9±0.6| 4.1±0.9| 4.1±0.4| 6.6±2.0| 14.7±9.4 |
| c_tr                           | 4.2±0.4| 4.1±0.4| 3.9±0.6| 4.8±0.7| 4.7±0.7| 7.0±1.4 |
| Abd                            |      |      |      |      |      |      |
| c_app                          | 3.6±0.5| 2.9±0.6| 5.6±0.9| 5.1±1.4| 14.6±2.7| 18.4±4.0 |
| c_tr                           | 3.1±0.2| 3.3±0.6| 5.2±0.5| 5.6±1.4| 7.0±1.4| 9.4±1.5 |
| Iliac                          |      |      |      |      |      |      |
| c_tr                           | 3.2±1.0| 2.6±0.7| 5.2±0.8| 5.0±1.6| 8.9±2.0| 28.5±10 |
| c_tr                           | 2.9±0.7| 3.1±0.9| 5.3±0.3| 5.5±1.1| 8.7±3.0| 17.5±7.5 |

*p<0.05

Group 1, Normotensive control animals; Group 2, hypertensive animals. c_app, mean apparent phase velocity; c_tr, foot-foot pulse-wave velocity, both given in meters per second.
COMPARISON OF SYSTEMIC COMPLIANCE WITH PULSE WAVE VELOCITY ($c_{ff}$)

FIGURE 8. A comparison of systemic compliance and pulse-wave velocities by the foot-foot method at low control and high pressure levels.

became markedly discordant consistent with strong local reflections. The discordance in $c_{ss}$ vs. $c_{ff}$ was more pronounced in Group 2 than Group 1 in the thoracic, abdominal, and iliac arterial segments ($14.7\pm 9.4$ vs. $7.0\pm 1.4$; $18.4\pm 4.0$ vs. $9.4\pm 1.5$; $28.5\pm 10$ vs. $17.5\pm 7.5$ m/sec respectively; $p<0.05$ for each). Local reflection coefficients ($\Gamma_L$) at the level of the renal artery branches were similar for Groups 1 and 2 at control pressures, whereas, at the terminal aortic bifurcation, $\Gamma_L$ was significantly increased for Group 2 compared with Group 1 controls ($0.26\pm 0.16$ vs. $0.06\pm 0.2$; $p = 0.01$). At hypertensive pressures, $\Gamma_L$ at the junction of the renal artery branches was significantly increased for Group 1 compared with Group 2 ($0.27\pm 0.03$ vs. $0.15\pm 0.07$; $p = 0.02$). Reflection at the terminal aortic bifurcation was significantly lower for Group 1 than for Group 2 ($0.23\pm 0.17$ vs. $0.45\pm 0.16$; $p = 0.03$).

The average aortic input impedance is given in Figures 6A and 6B. There was a tendency for the characteristic impedance to remain constant across the range of pressure tested (Table 2). At elevated pressures, characteristic impedance for the hypertensive animals was significantly elevated over controls ($160\pm 24$ vs. $128\pm 22$ d $s$ cm$^{-2}$; $p<0.05$). Systemic compliance was calculated using the three-element Windkessel or two-element (RC) model (low pressure only) for each pressure level studied (see Figure 7). Compliances at high pressures were similar for Group 1 and Group 2 ($0.16\pm 0.09$ vs. $0.25\pm 0.12$ ml/mm Hg; $p<0.05$) but were significantly higher at control pressures ($0.96\pm 0.09$ vs. $0.49\pm 0.16$ ml/mm Hg; $p<0.05$) and at low mean pressures ($1.41\pm 0.24$ vs. $0.62\pm 0.26$ ml/mm Hg; $p<0.002$).

Characterization of the ventricular/vascular interaction by determination of effective arterial elastance ($E_a$) from pressure-volume relations showed differences similar to those found by comparison of compliances between Groups 1 and 2. When expressed as the reciprocal ($1/E_a$) in terms of compliance (ml/mm Hg), values of $1/E_a$ at elevated mean pressures were similar for hypertensive and control groups ($0.48\pm 0.08$ vs. $0.85\pm 0.44$ ml/mm Hg; $p = 0.06$) but reduced for the hypertensive animals at control ($0.96\pm 0.12$ vs. $1.83\pm 0.75$ ml/mm Hg; $p<0.02$) and low pressures ($1.47\pm 0.26$ vs. $3.19\pm 1.51$ ml/mm Hg; $p<0.05$). When plotted as a function of mean pressure, values of $1/E_a$ followed a parallel relation to systemic compliance as a function of pressure (see Figures 2 and 7). Ventricular/vascular coupling was also assessed with a determination of pulsatile power and also total power from Fourier data. Average power was increased by 11% in the hypertensive group at high pressures compared...
TABLE 4. Histological Data for Hypertensive and Normotensive Control Animals

<table>
<thead>
<tr>
<th>Location</th>
<th>Hypertensive</th>
<th>Normotensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thickness (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASC</td>
<td>1.2±0.10</td>
<td>1.07±0.18</td>
</tr>
<tr>
<td>PRD</td>
<td>0.94±0.26</td>
<td>0.87±0.18</td>
</tr>
<tr>
<td>LTH</td>
<td>0.77±0.15</td>
<td>0.76±0.18</td>
</tr>
<tr>
<td>ABD</td>
<td>0.65±0.15</td>
<td>0.66±0.19</td>
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<tr>
<td>Lamellae #</td>
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</tr>
<tr>
<td>ASC</td>
<td>47.2±4.1</td>
<td>48±3.8</td>
</tr>
<tr>
<td>PRD</td>
<td>46±4.6</td>
<td>35.8±3.8*</td>
</tr>
<tr>
<td>LTH</td>
<td>24.6±9.3</td>
<td>24.5±3.1</td>
</tr>
<tr>
<td>ABD</td>
<td>12.0±2.1</td>
<td>11.5±2.9</td>
</tr>
<tr>
<td>Internal diameter (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASC</td>
<td>1.3±0.13</td>
<td>1.39±0.20</td>
</tr>
<tr>
<td>PRD</td>
<td>1.09±0.11</td>
<td>1.20±0.19</td>
</tr>
<tr>
<td>LTH</td>
<td>0.79±0.17</td>
<td>1.06±0.32</td>
</tr>
<tr>
<td>ABD</td>
<td>0.60±0.17</td>
<td>0.80±0.25</td>
</tr>
<tr>
<td>Collagen content (µg/mg dry)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASC</td>
<td>26.78±1.98</td>
<td>27.12±1.9</td>
</tr>
<tr>
<td>ABD</td>
<td>38.08±5.9</td>
<td>31.95±6.2</td>
</tr>
</tbody>
</table>

ASC, ascending aorta; PRD, proximal descending just distal to left subclavian origin; LTH, thoracic aorta (1 cm proximal to celiac trunk); ABD, abdominal aorta.

*p<0.05; t*p<0.01; NS, not significant.

Discussion

We have studied the effect of acute changes in mean arterial pressure on characteristics of ventricular/vascular coupling dynamics and regional pulse transmission properties in normotensive controls and in a chronically hypertensive baboon model. Our data demonstrated that pulse-wave velocities in distal aortic segments at high pressures and systemic compliance or estimates of effective arterial elastance at low and control pressures revealed large vessel stiffening in the aortas of chronically hypertensive baboons compared with normotensive controls (see Figure 8). Furthermore, we found that changes in regional arterial dynamics in the hypertensive baboon model paralleled histological structural alterations of the tunica media (thickness of lamellae, collagen content) of the vascular wall. These histological abnormalities increased from proximal to more distal aortic segments compared with controls in similar fashion to regional differences in pulse-wave velocity, suggesting hypertensive changes in the systemic tree progress from distal toward proximal vascular segments.

It has been known for many years that the vascular changes associated with hypertension result in changes in the aortic pressure waveform. Prior to availability of sphygmomanometry, hypertension was diagnosed by a pulse that had a smooth diastolic decay from a substantial peak and remained palpable throughout the entire diastolic period. Invasive studies in hypertension demonstrated an increase in pulse pressure with a prominent late systolic peak and loss of the dicrotic wave. In this setting, proximal aortic waveforms tended to assume the contour of more distal waveforms. We have previously reported the characteristics of pressure waveforms along the normotensive baboon aorta that suggested little reflection was manifested on proximal aortic waveforms. In the current study, waveforms were similar at hypertensive and control pressures for both hypertensive and normotensive groups. At elevated pressures a pronounced "diastolic ringing" was observed in distal waveforms of the hypertensive animals (see...
Figure 5). It is probable that these diastolic oscillations represent increased reflection in distal aortic segments and terminal branches. These data are consistent with the finding of increased wall thickness and reduced internal luminal diameter in the hypertensive subset. This is further supported by a 100% increase in estimates of local reflection coefficients at the terminal aortic bifurcation in the hypertensive group compared with controls.

The regional wave speeds were similar for both groups at control and low pressure levels. These data are consistent with previous early work that showed pulse-wave velocity in hypertensive subjects was not increased when blood pressure was controlled. In our primate study groups, the wave velocities were increased in more distal aortic segments in the hypertensive animals compared with controls at elevated mean pressures. This would suggest that the vascular adaptations to chronic hypertension are more pronounced in distal aortic segments and progress proximally. Pulse-wave velocity has been used as a noninvasive technique to discriminate hypertensive subjects from controls, presumably due to a decreased arterial compliance in this population. Despite reduced compliance compared with controls at normal or hypotensive pressures, wave speeds only discriminated hypertensive baboons during elevated mean arterial pressures. The discrepancy with previous clinical trials may be partially related to the fact that noninvasive carotid and femoral Doppler techniques to determine pulse-wave velocity have more contribution from the medium-sized arterial branches of the aorta, in contrast to our study in which regional wave speeds are principally confined to the aorta. Our results strongly suggest that it is important that clinical study populations be compared at similar mean arterial pressures since this variable alone strongly affects differences in pulse-wave velocity in hypertensive subjects compared with controls.

Compliance was determined in our study by a three-element Windkessel model (see Figure 3) with the input pressure and flow or a monoequivalent RC model at the lowest pressures. Using these techniques, we found that systemic compliance at elevated pressures was similar for both groups even though distal wave speeds were significantly increased in the hypertensive group compared with controls. It is possible that the method of determining compliance by a three-element electrical analog for circulation is more sensitive to the proximal aortic vascular properties (which affect the input flow waveform) and represents an effective systemic compliance. Therefore, a determination of local compliance (from wave speeds and diameter) in the abdominal aorta may be more accurate for discriminating regional hypertensive structural adaptation.

The literature is contradictory on the role of systemic arterial compliance in isolated hypertension. For example, some investigators suggest reduced arterial compliance and altered vascular elasticity may be a primary factor in the clinical manifestation of hypertension. Other investigators have shown that central aortic compliance probably has no significant causative role in isolated systolic hypertension. Changes secondary to chronic hypertensive stress mainly occur, however, in the distal aorta and terminal branches. Ventricular/vascular coupling was evaluated by the ratio of pulsatile to total power similar to previous work as well as by analysis of the end-systolic pressure-volume relation. The ratio of pulsatile/total power has been shown to be increased in hypertensive human subjects in which mean blood flow was maintained. Our hypertensive baboons had significant cardiac hypertrophy, and cardiac output fell when pressures were pharmacologically elevated, resulting in a lower pulsatile power. Thus, pulsatile/total power failed to discriminate the hypertensive animals with left ventricular hypertrophy. The clinical implication is that this ratio may not be different in hypertensive man compared with controls if significant hypertensive heart disease is present. In this setting, the reduced pulsatile/total power ratio does not imply improved efficiency of ventricular/vascular coupling but rather suggests left ventricular systolic dysfunction.

The second method applied to describing the ventricular/vascular interaction was determined from the end-systolic pressure-volume relations at each pressure level tested. Effective ventricular elastance represents the generally linear function of the end-systolic pressure-volume relation, and effective arterial elastance represents the slope of a line drawn from any point along the plot of effective ventricular elastance to the end-diastolic volume corresponding to that beat. We found that the hypertensive ventricular end-systolic pressure-volume relation was shifted to the left, giving lower end-systolic volumes compared with controls. Slopes of the control and hypertensive ventricular elastance were similar (Figure 1). The reciprocal of the arterial elastance (1/E) as a function of mean aortic pressure was similar to total systemic compliance as a function of mean arterial pressure (Figure 2). This index of ventricular/vascular coupling correctly distinguished hypertensive animals from controls at low and normotensive pressures. It has been shown that characteristic impedance in dogs was relatively independent of changes in mean arterial pressure over a limited range. Similarly, our data revealed little difference in characteristic impedance between controls and the hypertensive group except at elevated pressure levels. The findings at hypertensive pressures probably reflect the differences in regional vascular structural adaptation. These data are consistent with the study of Ting et al., where difference between control and hypertensives was eliminated by vasodilatation.

Structural alterations of the macrovasculature occur with age and chronic hypertension.
has been shown that there is also an age-dependent gradient of elastin-collagen across the vessel wall. Hypertension is known to affect the structural characteristics of the vascular wall as well, but recent investigation suggests that all vessels of the systemic tree may not be affected in similar and equal fashion. Lee and Smeda demonstrated in a hypertensive rat model that changes in some vascular beds were primary changes, whereas changes in the aorta and superior mesenteric artery were secondary effects.

We found a significantly greater number and increased thickness of elastic lamellae in descending and abdominal aortic segments in hypertensive animals. Also, the thickness of elastic lamellae and smooth muscle content was increased in the thoracic and abdominal aorta, respectively, in hypertensive animals compared with normotensive controls. There was an increase in collagen content in the distal aortic segments of the hypertensive group compared with the proximal aorta but not in controls. The stiffening of the aorta in hypertensive animals (indicated, for example, by decreased compliance) is not only a passive effect of the elevated pressure and nonlinear elasticity, but also a result, in part, of morphological changes in that vessel. The discordant velocities between groups in the abdominal aorta at elevated pressures may be a result of an increase in collagen and smooth muscle content.

Critique of Method

The ideal study would compare in vivo regional hemodynamics with histological examination, which precludes these investigations in man. We have chosen the baboon as a nonhuman primate model for secondary hypertension and ventricular hypertrophy and have previously compared regional arterial dynamics in the normotensive baboon to those found in man. This model has limitations in that the cardiac catheterizations had to be performed under halothane anesthesia. Halothane is known to possess cardiodiessant and peripheral vasodilatory effects. The aortas were not perfusion-fixed under pressure which precluded a more accurate analysis of regional wall thickness. The hypertensive state was surgically induced and only present for three and one half years. Although this reflects approximately one sixth of this primate's captivity lifespan, it may not be effectually equivalent to 12 years (one sixth of a 72-year lifespan) of hypertension in man. The authors are grateful to Mrs. Margaret Latham for creation of the graphics and Ms. Jean Gibbs for preparation of this manuscript. We are also grateful to David Cragg and David Weaver for their technical assistance.

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