Mechanoelastic Properties of the Aorta in Chronically Hypertensive Conscious Rats

LISETE C. MICHELINI, PH.D., AND EDUARDO M. KRIEGER, M.D.

SUMMARY The relationship between aortic caliber (AC) and aortic pressure (AP) was studied in eleven normotensive (NCR) and 17 one-kidney, one clip chronic renal hypertensive conscious Wistar rats (RHR) at rest and when transient changes in blood pressure were produced. The mean values for AC, AP, and tangential stress were 20%, 75%, and 73% higher in RHR than NCR. Similarly, the aorta thickness was 21% greater but radius/thickness was unchanged. Pulse pressure increased by 51%, and aortic pulsation was twice that of NCR. At control pressure, dynamic as well as mean distensibility of the aorta tended to be greater in RHR, but not statistically different. During transient changes in pressure, −40 to +40 mm Hg from control levels, dynamic distensibility was the same for both groups, but, at hypotensive levels, mean distensibility decreased significantly in NCR. Mean distensibility was related to distending pressure; an overlap of NCR and RHR values occurred between 130 and 160 mm Hg. At the pressures studied, the dynamic strain of RHR was markedly elevated because aortic pulsation (142%) increased more than caliber (20%). In spite of this, mean strain was similar for both groups. Therefore, RHR responded to a pressure change with a greater change in mean caliber which was proportional to their larger control caliber. Alterations in pressure caused greater changes in the absolute values of diastolic caliber than pulsation for both groups. These properties of the aortic wall appear to be important for baroreceptor resetting in hypertension.

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KEYWORDS • stress • strain • distensibility • stiffness • aortic caliber • wall thickness • electrolytic transducer • baroreceptor resetting • hypertension

It is well established that baroreceptors are reset to operate at the higher pressure level during hypertension.1 Resetting lags behind the increase in pressure and requires 1–2 days for completion in the rat. It has not yet been established whether resetting is due to changes in mechanical properties of the arterial wall or to changes in the receptors themselves. Alterations of the viscoelastic properties of the arterial wall can change the strain of the vessel and the deformation of the baroreceptors. Therefore, resetting in hypertension has been attributed to reduced distensibility,8,9 and thus stiffness of the arterial wall is generally considered to be increased.7–9 However, decreased stiffness has also been reported for vessels of DOCA- and renal-hypertensive rats.5,9 At control pressure, renal-hypertensive rabbits exhibited normal distensibility.4 Studies on spontaneously hypertensive rats18 have not demonstrated changes in wall distensibility but have emphasized the role of uncoupling the receptors from the vessel wall and/or changes in the sensitivity of the baroreceptors themselves in accounting for the resetting. The recent development of a new electrolytic strain gauge11,12 for the continuous measurement of aortic caliber in unanesthetized animals permitted us to compare the properties of the aorta in normotensive and renal hypertensive rats under physiological conditions.

Methods

Male Wistar normotensive (NCR, n = 11) and chronic (1–2 months) one-kidney, one clip hypertensive rats (RHR, n = 17) of similar age and weighing 200–250 g were studied. Aortic caliber was measured with an electrolytic strain gauge implanted into the first portion of the thoracic descending aorta 4 days before the experiment. Details of the construction and calibration of the transducer, as well as the surgical procedures for implantation, have been given.11,12 Aortic blood pressure was recorded with a plastic cannula (PE 10 connected to PE 50) inserted through the left carotid artery 1 day before. Systolic/diastolic and mean values for aortic caliber and pressure of conscious unrestrained rats were recorded simultaneously on a Hewlett-Packard (7848A) during the resting...
state and during transient alterations in blood pressure. Pressure changes were produced by the removal and infusion of blood from the femoral artery or by intravenous bolus injection (femoral vein) of norepinephrine, acetylcholine, and sodium nitroprusside. The doses of each pressor substance were selected to produce a 10 to 40 mm Hg change in pressure. Similar results were obtained when pressure was changed by blood or vasoactive substances. This similarity was also reported by Pagani et al.11 in studies on sheep. At the end of the experiment, under ether anesthesia, the aorta was fixed by perfusion with a modified Schlessinger solution to avoid retraction, and the thickness of the vessel wall (δ) was determined by morphometry.

The behavior of the aortic wall and its mechanoeelastic properties were determined by correlating pressure with caliber and using the data to calculate stress (σ), strain (ε), distensibility (calculated from Ep), and stiffness (Einc). For these calculations the aortic wall was assumed to be a homogenous elastic medium, having isotrophy and incompressibility, with a Poisson ratio of 0.5. The parameters referring to the tangential direction were calculated by the following formulas:4, 5, 14

\[ \sigma = P \times \frac{r}{\delta} ; \epsilon = \frac{\Delta C}{C} ; \text{Ep} = \frac{\Delta P \times C}{\Delta C} ; \]

\[ \text{Einc} = \frac{\Delta \sigma \times C}{\Delta C} \times 0.75, \]

where P is the mean pressure, r is the mean radius, ΔC is the displacement of mean caliber (C) during a mean pressure change (ΔP). The present measurements of pressure and caliber also permitted us to calculate the elastic properties of the aorta during the cardiac cycle, i.e., dynamic stress (σdyn), strain (εdyn), distensibility (Epdyndyn), and stiffness (Eindyn). The formulas employed were the same, but instead of using the changes in mean caliber and pressure, pulsatile values were used for each pressure level. As proposed by Peterson et al.4 for arteries in vivo, we used the “pressure elastic modulus” (Ep) as the operational measure of vessel stiffness, i.e., the reciprocal of distensibility.

Results are reported as means ± SEM. The statistical significance of differences between groups or within one group was analyzed by the unpaired and paired t tests (*p < 0.05).

Control Measurement

Figure 1 illustrates simultaneous recordings of intracardiac pressure and aortic caliber performed in conscious unrestrained NCR and RHR for periods ranging from 45 to 60 minutes. There was excellent agreement for both groups between the caliber and pressure curves, indicating that the electrotytic transducer accurately measures the aortic caliber continuously in awake animals, as documented previously.11, 12

As shown in table 1, the mean arterial pressure of RHR was 75% higher and the mean aortic caliber was 20% greater than for NCR. The pulse pressure (ΔP) was 51% higher for RHR and the aortic pulsation (ΔC) was twice that observed for NCR. The thickness of the aorta (δ) was significantly increased (21%) in RHR, but the mean radius/wall thickness ratio (r/δ) remained unchanged. There was no difference in heart rate in either group. The elastic properties of the aorta of NCR and RHR in the resting state are compared in table 1. The values for mean stress (σ), dynamic stress (σdyn), and dynamic strain (εdyn) were 73%, 49%, and 97% higher for RHR than for NCR rats. When compared to NCR, the aorta of RHR exhibited a slight but not significant increase in dynamic distensibility (Epdyndyn); the dynamic stiffness of the hypertensive wall was slightly decreased but the values for RHR and NCR were not statistically different.

Transient Alterations in Blood Pressure

The behavior of the aortic caliber and the mechanical properties of the aorta were studied during transient alterations in blood pressure. Arterial pressure was changed from control values of 113 ± 3 mm Hg for NCR and 178 ± 8 mm Hg for RHR in steps of 10 mm Hg over the range -40 to +40 mm Hg.

Figure 2 shows the alterations in mean aortic caliber produced by changes in mean arterial pressure. The caliber was expressed as percent changes from the control caliber for each animal, since there was great variability among individual values (6.019 to 7.221 mm in NCR and 7.418 to 8.575 in RHR). The curves relating pressure to caliber were similar, except that those for RHR were shifted to the right. The values for RHR were between 140 and 210 mm Hg, while those for NCR were in the 100-125 mm Hg range. The mean slope of the curves was 1.10 ± 0.24 and 1.27 ± 0.09 × 10⁴ mm/mm Hg for NCR and RHR, respectively, with high positive correlation coefficients of 0.90 ± 0.02 and 0.93 ± 0.02. In the pressure range analyzed, four RHR and two NCR curves exhibited flattening at the highest distending pressure. All the other curves behaved as theoretically predicted for the pressure-caliber relationship of elastic arteries.

When blood pressure was altered ± 40 mm Hg in relation to control values, the mean stress (fig. 3 D) increased progressively in both groups. The slopes of the curves were identical, but RHR were shifted to higher values (average increase of 56%). In spite of this, the mean strain, which changed markedly with pressure, was the same for both groups (fig. 3 E). The mean strain for RHR did not change because they exhibited a larger response to pressure which was proportional to their larger control caliber. Alterations in pressure produced minor changes in mean RHR distensibility (fig. 3 F). The distensibility of NCR decreased significantly when blood pressure was reduced and showed only a tendency (not statistically significant) to increase with pressure elevation. The aorta of RHR tended to be more distensible than that of NCR, but the differences were not statistically significant except
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Figure 1. Simultaneous recordings of pulsatile and mean aortic blood pressure (top) and pulsatile and mean aortic caliber (bottom) in conscious normotensive and hypertensive rats at different recording speeds. A schematic diagram demonstrating the positions in the aorta of the electrolytic strain gauge and the arterial cannula is shown at the left.

Table 1. Control Measurements in Conscious Unrestrained Normotensive Rats (NCR) and Renal Hypertensive Rats (RHR)

<table>
<thead>
<tr>
<th>Aorta measurements</th>
<th>NCR (n = 11)</th>
<th>RHR (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pressure</strong></td>
<td></td>
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<tr>
<td>AP (mm Hg)</td>
<td>128 ± 3/77 ± 3</td>
<td>217 ± 7* / 140 ± 5*</td>
</tr>
<tr>
<td>(101 ± 3)</td>
<td>(177 ± 6)*</td>
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<tr>
<td><strong>Pulse pressure</strong></td>
<td></td>
<td></td>
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<tr>
<td>ΔP (mm Hg)</td>
<td>51 ± 2</td>
<td>77 ± 4*</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
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<tr>
<td>HR (bpm)</td>
<td>409 ± 9</td>
<td>412 ± 12</td>
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<tr>
<td><strong>Caliber</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC (mm)</td>
<td>6.557 ± 0.128 / 6.533 ± 0.128</td>
<td>7.889 ± 0.099* / 7.832 ± 0.098*</td>
</tr>
<tr>
<td>(6.545 ± 0.128)</td>
<td>(7.859 ± 0.099)*</td>
<td></td>
</tr>
<tr>
<td><strong>Pulsation</strong></td>
<td>0.024 ± 0.001</td>
<td>0.058 ± 0.006*</td>
</tr>
<tr>
<td>ΔC (mm)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Wall thickness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>δ(μM)</td>
<td>84.01 ± 2.00</td>
<td>101.55 ± 2.51*</td>
</tr>
<tr>
<td><strong>Radius/thickness</strong></td>
<td>12.51 ± 0.51</td>
<td>12.36 ± 0.33</td>
</tr>
<tr>
<td>r/δ</td>
<td></td>
<td></td>
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<td><strong>Wall stress</strong></td>
<td></td>
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<tr>
<td>σ(×10^6 dyne/cm²)</td>
<td>1.69 ± 0.10</td>
<td>2.92 ± 0.12*</td>
</tr>
<tr>
<td><strong>Dynamic stress</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>σdyn(×10^6 dyne/cm²)</td>
<td>0.85 ± 0.05</td>
<td>1.27 ± 0.09*</td>
</tr>
<tr>
<td><strong>Dynamic strain</strong></td>
<td></td>
<td></td>
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<tr>
<td>εdyn(%)</td>
<td>0.37 ± 0.02</td>
<td>0.73 ± 0.08*</td>
</tr>
<tr>
<td><strong>Dynamic distensibility</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epdyn(×10^6 dyne/cm²)</td>
<td>19.12 ± 1.50</td>
<td>16.08 ± 1.64</td>
</tr>
<tr>
<td><strong>Dynamic stiffness</strong></td>
<td></td>
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<tr>
<td>Eindyn(×10^6 dyne/cm²)</td>
<td>17.96 ± 1.60</td>
<td>14.38 ± 1.52</td>
</tr>
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</table>

*Significant (p < 0.05) when compared with control values.
The data presented in figure 3 B and E, expressed as percentages, show that changes in mean caliber are greater than changes in pulsation, suggesting that alterations in diastolic caliber were the most important single factor. This can be demonstrated unequivocally by considering the absolute values for aortic caliber. In response to an increase in pressure of 40 mm Hg, the systolic caliber of NCR and RHR increased 0.047 and 0.066 mm. The increase in diastolic caliber, 0.038 mm (NCR) and 0.053 mm (RHR), accounted for 81% and 80% of the total differences in systolic caliber. The pulsation increased by only 19% (0.009 mm) and 20% (0.013 mm) for NCR and RHR, respectively.

**Discussion**

The electrolytic strain gauge implanted in the animals to record the systolic, diastolic, and mean calibers permitted the analysis of the dynamic (pulsatile) as well as the mean values for stress, strain, distensibility, and stiffness of the aorta in awake rats. The data reported here show for the first time that under physiological conditions the pulsation of the aorta of the renal hypertensive rat was twice that of the normotensive rat in spite of the fact that distensibility and stiffness were similar.

In hypertensive rats, both the caliber and thickness of the aortic wall increased in the same proportion; therefore, the radius/thickness ratio was unchanged. Thus, the tangential wall stress increased only because of pressure elevation. The dynamic strain was markedly elevated in hypertension because the increase in aortic pulsation (142%) was much greater than the increase in caliber (20%). An interesting finding is that during transient changes in pressure the ratio of change of displacement of mean caliber/control caliber (mean strain) was similar in hypertensive and normotensive rats, suggesting the same "operating level" for both groups. Moreover, dynamic and mean distensibility were not different at resting conditions. This last result is in agreement with data reported for mean distensibility in renal hypertensive rabbits and in spontaneously hypertensive rats.

In the experiments reported here on conscious rats, the changes in pressure were ±40 mm Hg, and therefore extreme changes in pressure like those obtained in vitro were not produced. This may explain why only 2/7 NCR and 4/9 RHR showed the decrease in distensibility with increasing transmural pressure which increased and at +40 mm Hg was significantly elevated by 22% and 36% for RHR and NCR, respectively. The opposite was observed when the pressure was reduced: at —40 mm Hg there was a significant decrease of 25% (RHR) and 14% (NCR). When aortic pulsation was related to distending pulse pressure (fig. 3 C), the dynamic distensibility tended to be greater for RHR than NCR, but the differences were not statistically significant. For both groups, dynamic distensibility had a tendency to decrease when pressure fell. There was no significant difference between the groups in terms of dynamic stiffness (data not shown).

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Aortic Dynamics in Hypertension

Figure 3. Dynamic (top) and mean (bottom) mechanoeelastic properties of the aorta during transient changes in pressure (−40 to +40 mm Hg). A and D = stress; B and E = strain; C and F = distensibility. Symbols represent means, and vertical bars ± SE. * = significant difference (p < 0.05) between RHR and NCR, † = value significantly different (p < 0.05) from the control.

Figure 4. Alterations in mean distensibility (left) and mean stiffness (right) of the aorta in NCR (•) and RHR (○). Symbols represent means and vertical bars ± SE.

is usually reported in the literature. Increase in distensibility with pressure, observed in the majority of our experiments, has also been reported for dogs, cats, rabbits, and man when the changes in pressure were not extreme.

The displacement of the baroreceptor firing range to a new level lasts 1–2 days, whenever there is a permanent change in pressure in either direction, hypertension or hypotension. The baroreceptors in chronic renal hypertensive rats discharge in apparently normal fashion even though, as shown here, the aortic pulsation of these rats was twice the normal value. It is interesting to speculate that baroreceptors are also part of the adaptative changes in the aortic wall produced by hypertension and, therefore, in the new state of equilibrium achieved by the aortic wall (coincidentally, the aorta takes 1–2 days to dilate during acute hypertension — Michelini, L. C. and Krieger, E. M., unpublished results) the baroreceptors are normally activated even when the pulsation is greater. In this new resting position, the increase in firing produced by transient pressure elevation is determined mainly by stretching the diastolic caliber. This interpretation derives from another important finding in the present study, i.e., during transient alterations in pressure the major determinant for baroreceptor distortion was shown to be the displacement of diastolic caliber rather than vessel pulsation for both groups. The fact that the percentage of changes in diastolic caliber in relation to the control was the same for normotensive and hypertensive rats reinforces the
idea that adaptative mechanisms in the aorta compensate for the concurrent geometrical changes to maintain a nearly constant level of distensibility. This interpretation has been made by Pagani et al.\(^\text{18}\) to explain the same distensibility exhibited at baseline levels of aortic stress by adult and newborn sheep, although there are great differences in vessel wall geometry.

It is difficult to compare the present results with many others reported in the literature because of marked differences in species, techniques, experimental design, and method of calculation of arterial elasticity. The mean values for distensibility and stiffness reported here are greater than those described by Cox\(^\text{7}\) for rat carotid segments but similar to those reported by Berry and Greenwald\(^\text{1}\) for rat aorta in situ when the later values of \(E_{inc}\) in SI units \((\times 10^4 \text{ N/m}^2)\) are converted to CGS units \((\times 10^7 \text{ dyne/cm}^2)\). One possible explanation for the apparently high stiffness found in the intact rat is the significant aortic muscle tone.\(^\text{8}\) In fact, the aorta of the rat has several concentric muscular lamellae\(^\text{8}\) and, as stressed by Dobrin,\(^\text{8}\) the smooth muscle layer plays an important role in determining aortic stiffness in the physiological pressure range. Moreover, the aortic muscle of the rat seems to play an important role in maintaining the aortic caliber during the first few hours of acute hypertension.\(^\text{11}\)

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References

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