Characteristics of Single Aortic and Right Subclavian Baroreceptor Fiber Activity in Rabbits with Chronic Renal Hypertension

By Jennifer E. Angell-James

ABSTRACT

Experimental renal hypertension was induced in rabbits by wrapping polyethylene around one kidney and removing the other. The impulse activity in single baroreceptor fibers of the aortic nerves to the aortic arch and the right subclavian areas was studied 7-19 weeks postoperatively during nonpulsatile perfusion of an isolated aortic arch preparation. The results were compared with those obtained in normal rabbits. Curves relating the impulse frequency to the aortic arch pressure were constructed. In rabbits with hypertension, the threshold pressure of the aortic baroreceptor fibers was increased from a normal value of 52.5 ± 5.5 to 106.5 ± 5.8 mm Hg, and the point of inflection was increased from 112.4 ± 6.2 to 163.4 ± 5.1 mm Hg. The sensitivity of the baroreceptors to changes in pressure was reduced from 1.19 ± 0.14 to 0.64 ± 0.06 impulses/sec mm Hg⁻¹. Similar results were obtained for the right subclavian area. Hysteresis, as indicated by the separation of the curves produced by first increasing and then reducing the aortic pressure, was more evident in rabbits with hypertension than in normal rabbits. The changes in baroreceptor activity in rabbits with hypertension were associated with alterations in the mechanical properties of the arterial walls, which were demonstrated by the pressure-volume curves. Also, there were demonstrable histological lesions of the arterial walls and the receptors in rabbits with hypertension.

KEY WORDS pressure-volume curves baroreceptor nerve endings aortic arch pathology

McCubbin et al. (1) first demonstrated that the function of the baroreceptors is modified in experimental renal hypertension by making whole-nerve recordings of the carotid sinus and the aortic nerves of dogs. Their results were confirmed by recordings from the aortic nerves of rats (2) and rabbits (3). A resetting of the baroreceptors does occur during hypertension, but whole-nerve recordings in intact animals fail to show if it results from a true resetting of individual baroreceptor units, a loss of or an injury to the receptors, or a combination of both.

The experiments described in this paper were performed to study the physiological characteristics of individual aortic baroreceptor units in chronic experimental renal hypertension. Controlled perfusion of the isolated aortic arch allowed the mean aortic blood pressure, the pulse pressure, and the pulse frequency to be varied independently (4, 5).

Methods

PRODUCTION OF RENAL HYPERTENSION

In 18 New Zealand white rabbits (2.45 ± 0.12 kg) anesthetized with sodium pentobarbital (39.5 ± 3.02 mg/kg, iv), the left kidney was encapsulated in a polyethylene sheet and the right kidney was removed. In 9 rabbits, a polyethylene cannula was inserted into the renal artery at the time of the operation, and the mean blood pressure was recorded with a mercury manometer. The mean blood pressure of the unanesthetized rabbits was measured before the operation and at weekly intervals postoperatively with a Grant-Rothschild capsule (6) which had been modified by adding a light source for transillumination of the ear.

TERMINAL EXPERIMENT

Blood Pressure Measurements.—The mean blood pressure was measured with the capsule in 11 rabbits (3.4 ± 0.17 kg) 7-80 weeks postoperatively. In 6 of these rabbits the pressure was compared with that obtained with an electromanometer (Bell and Howell) connected to a catheter inserted under local anesthesia into the central artery of the ear. The signals were recorded after suitable amplification (4) on a multichannel ultraviolet recording oscillograph. The average difference between individual observations was 0.67 ± 1.5 mm Hg.
The rabbits were anesthetized with urethane (1.6 ± 0.06 g/kg, iv). A tracheostomy was performed and, after the administration of heparin (1000 IU/kg), the aortic arch pressure was recorded through a cannula which had been passed retrograde down the right common carotid artery. The estimated amplitude distortion of the catheter-manometer system was less than 5% up to about 25 Hz (7).

Isolation and Perfusion of the Aortic Arch Region.—The aortic arch region was isolated from the circulation and perfused with Krebs-Henseleit solution (37–39°C) through a cannula which had been passed through the wall of the left ventricle; the effluent drained out through the cannula in the right common carotid artery. Perfusion was carried out using nonpulsatile pressure, and the mean blood pressure in the aorta was measured via a Sterivac polyethylene cannula. Full details of this method have been described elsewhere (4, 5, 8).

Single- or few-fiber recordings were made from the aortic nerves using saline-wick silver-silver chloride electrodes connected to a Tektronix 122 preamplifier. After suitable amplification, the recordings were displayed on ultraviolet light sensitive paper (4, 5).

The methods for analysis of the threshold pressure, the threshold index, the gradient of the first part of the curve relating impulse frequency to aortic arch pressure, and the point of inflection have been described previously (5). Statistical analysis was applied to this data (5), and the relationship between the baroreceptor activity, the arterial blood pressure, and the time postoperatively that the experiments were performed was estimated by calculating the regression line which was weighted to include the number of fibers represented in a mean value.

Pressure-Volume Curves.—Pressure-volume curves of the perfused area were obtained by injecting known volumes of Krebs-Henseleit solution at 37–38°C into the side arm of the aortic cannula and recording peak pressure. The initial volume of the perfused vascular territory at 0 mm Hg was measured by aspiration of the fluid contents. Because of inevitable small leaks in each preparation it was not possible to assess the steady-state pressure. However, the corresponding fluid volume in each rabbit was injected at the same rate. The pressure was plotted against the injected volume expressed as a percent of the original volume of fluid in the aorta at zero pressure to compensate for the differences between specimens in the initial volume of the vascular bed under study.

HISTOLOGY

Histological studies were performed on 15 rabbits 3–109 weeks postoperatively when their mean blood pressure varied from 125 to 200 mm Hg. The following specimens were fixed in 10% formal-sucrose and embedded in wax: the right subclavian artery, the right carotid sinus, the ascending aorta, the upper part of the descending thoracic aorta, and the aortic arch. The sections were stained with hematoxylin and eosin, Verhoeff's and Van Gieson's solutions, and Gomori's, Orcein/hemalum, Masson, toluidine blue, Rhinehardt's colloidal iron (CI), Mallory's phosphotungstic acid-hematoxylin (PTAH), Von Kossa's, and reticulin stains.

Histochemical studies of the nerve endings in the left carotid sinus and the middle of the aortic arch were performed with a modification of the Koelle technique (9).

Results

EFFECT OF RENAL ENCAPSULATION ON ARTERIAL BLOOD PRESSURE

In 15 rabbits the blood pressure rose from a control level of 84.1 ± 3.1 mm Hg to a peak value of 170.1 ± 4.5 mm Hg within 2–20 weeks after operation. The blood pressure then began to fall in some rabbits, but in others it remained relatively constant. However, blood pressure was very labile, and an average change in mean blood pressure of 30 mm Hg (range 20 to 45 mm Hg) was recorded in 3 rabbits during small movements. In normal rabbits the maximum change was 15 mm Hg.

Of 18 rabbits subjected to renal encapsulation, 7 died of hypertension or postoperative complications. The remaining 11 rabbits were used in the terminal experiment. They had a mean aortic blood pressure of 161.1 ± 7.1 mm Hg. Their systolic pressure (191.5 ± 9.7 mm Hg), diastolic pressure (142.2 ± 6.1 mm Hg), pulse pressure (50.5 ± 6.0 mm Hg), and heart rate (297.1 ± 54.4 beats/min) were all higher than the corresponding values in normal rabbits.

ISOLATED AORTIC ARCH PREPARATION

The physiological characteristics of baroreceptors from the aortic arch and the right subclavian artery were studied in 11 rabbits with renal hypertension, and single-fiber preparations were obtained from 9 rabbits. The results were compared with those obtained from a control group of 17 normal rabbits (5, 8).

Aortic Arch Baroreceptors.—On raising the aortic arch pressure from zero, the average threshold pressure of 71 fibers from the left aortic nerve of eight rabbits with renal hypertension was 106.5 ± 5.8 mm Hg compared with 52.5 ± 5.5 mm Hg for normal rabbits (P < 0.001) (Table 1). There was, however, a large variation in the threshold pressure for individual fibers, predominantly in the hypertensive group of rabbits (Fig. 1). As seen in Figure 1, the majority of the fibers in rabbits with hypertension had threshold pressures in excess of 80 mm Hg; those in the normal rabbits had lower thresholds. The results from individual experiments are given in Table 2.

Although the threshold frequency of many of the fibers studied in the rabbits with renal hypertension...
TABLE 1
Comparison of the Characteristics of the Impulse Activity in Single- and Few-Fiber Preparations of Baroreceptor Fibers from the Left and the Right Aortic Nerves of Normal Rabbits and Rabbits with Renal Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Left aortic nerve experiments</th>
<th>Right aortic nerve experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Renal hypertension</td>
</tr>
<tr>
<td>No. rabbits</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.2 ± 0.12</td>
<td>2.3 ± 0.15</td>
</tr>
<tr>
<td>Experimental</td>
<td>3.3 ± 0.22</td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>87.5 ± 5.6</td>
<td>76.0 ± 5.1</td>
</tr>
<tr>
<td>Peak*</td>
<td>173.8 ± 5.1</td>
<td>183.0 ± 6.4</td>
</tr>
<tr>
<td>Experimental*</td>
<td>160.3 ± 7.9</td>
<td>180.0 ± 7.9</td>
</tr>
<tr>
<td>No. fibers</td>
<td>29</td>
<td>71</td>
</tr>
<tr>
<td>Threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td>52.5 ± 5.5</td>
<td>106.5 ± 5.8</td>
</tr>
<tr>
<td>Frequency (impulses/sec)</td>
<td>34.1 ± 2.3</td>
<td>32.6 ± 2.4</td>
</tr>
<tr>
<td>Index (impulses/sec mm Hg^-1)</td>
<td>2.89 ± 2.1</td>
<td>0.45 ± 0.07</td>
</tr>
<tr>
<td>Gradient (impulses/sec mm Hg^-1)</td>
<td>1.19 ± 0.14</td>
<td>0.64 ± 0.06</td>
</tr>
</tbody>
</table>

Values are means ± s.e.
*Weeks after surgery are given in parentheses.

was lower than that in normal rabbits despite the elevated threshold pressures in the rabbits with hypertension (Table 1), the mean impulse frequency at the mean threshold pressure was only slightly lower than normal. The threshold index was therefore much lower in the rabbits with hypertension (Table 1).

The types of discharge of impulses at the threshold were similar to those described previously in the normal rabbit (5). In the rabbits with renal hypertension, 66.2% of the fibers had a type 1 critical threshold below which there was no discharge compared with 65.5% in the control group; increasing the pressure above this point produced an increase in discharge frequency which was linearly related to pressure. Intermittent discharge (type 2), was observed in 18.3% of the fibers from rabbits with renal hypertension compared with 13.8% in the normal rabbits. The plateau-type threshold (type 3), in which the discharge frequency did not increase with pressure immediately but only after a further pressure rise of up to 40 mm Hg in the normal rabbits and up to 100 mm Hg in the rabbits with hypertension, occurred in 15.5% of the fibers from rabbits with renal hypertension.
hypertension compared with 20.7% in the normal rabbits.

As the aortic arch pressure was increased above the threshold pressure, there was usually an initial linear relationship between the impulse frequency and the aortic arch pressure, but some fibers from the rabbits with renal hypertension discharged irregularly at most pressures. At a higher pressure, the curve began to flatten and form a plateau at the point of inflection (Fig. 2), and in some fibers the impulse discharge diminished. A typical record of a single active baroreceptor fiber from a rabbit with renal hypertension is illustrated in Fig. 3. However, there was an enormous variation in the characteristics of different fibers.

The gradient of the first part of the curve relating the impulse frequency to the pressure was significantly less in the rabbits with renal hypertension than it was in the normal rabbits ($0.64 \pm 0.06$ and $1.19 \pm 0.14$ impulses/sec mm Hg$^{-1}$, respectively, $P < 0.001$) (Table 1).

In all experiments there was an elevation of the threshold pressure and a flattening of the curve (Table 2, Fig. 4). The point of inflection was significantly elevated ($P < 0.001$), but this increase

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### Table 2

Data Obtained from Individual Rabbits with Experimental Renal Hypertension in Which Recordings Were Made from the Left Aortic Nerve

<table>
<thead>
<tr>
<th>Rabbit no.</th>
<th>1</th>
<th>5</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>13</th>
<th>17</th>
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<tr>
<td>Weight (kg)</td>
<td>2.9</td>
<td>2.6</td>
<td>2.6</td>
<td>2.5</td>
<td>2.3</td>
<td>1.9</td>
<td>1.8</td>
<td>2.9</td>
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<tr>
<td>Control</td>
<td>90</td>
<td>100</td>
<td>65</td>
<td>75</td>
<td>110</td>
<td>95</td>
<td>95</td>
<td>70</td>
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<td>Peak*</td>
<td>165</td>
<td>190</td>
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<td>165</td>
<td>170</td>
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<td>175</td>
<td>195</td>
</tr>
<tr>
<td>Threshold</td>
<td>115</td>
<td>102</td>
<td>118</td>
<td>90</td>
<td>117.4</td>
<td>84.3</td>
<td>121</td>
<td>137.5</td>
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<tr>
<td>No. fibers</td>
<td>10</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>25</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td>102</td>
<td>95</td>
<td>113.8</td>
<td>90</td>
<td>117.4</td>
<td>84.3</td>
<td>121</td>
<td>137.5</td>
</tr>
<tr>
<td>Frequency (impulses/sec)</td>
<td>19.6</td>
<td>29.1</td>
<td>24.1</td>
<td>28.3</td>
<td>41.6</td>
<td>38.7</td>
<td>23</td>
<td>47.5</td>
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<tr>
<td>Index (impulses/sec mm Hg$^{-1}$)</td>
<td>0.22</td>
<td>0.31</td>
<td>0.42</td>
<td>0.52</td>
<td>0.59</td>
<td>0.55</td>
<td>0.18</td>
<td>0.35</td>
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<td>Gradient (impulses/sec mm Hg$^{-1}$)</td>
<td>0.48</td>
<td>1.04</td>
<td>0.36</td>
<td>0.7</td>
<td>0.71</td>
<td>0.73</td>
<td>0.27</td>
<td>0.38</td>
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<td>Point of inflection</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>20</td>
<td>5</td>
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<td>2</td>
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<tr>
<td>No. fibers</td>
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<td>164.9</td>
<td>180</td>
<td>155</td>
<td>160.3</td>
<td>145</td>
<td>176.7</td>
<td>157.5</td>
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<tr>
<td>Pressure (mm Hg)</td>
<td>154.9</td>
<td>164.9</td>
<td>180</td>
<td>155</td>
<td>160.3</td>
<td>145</td>
<td>176.7</td>
<td>157.5</td>
</tr>
<tr>
<td>Frequency (impulses/sec)</td>
<td>57.9</td>
<td>103</td>
<td>83.8</td>
<td>44.7</td>
<td>71.9</td>
<td>72</td>
<td>43.7</td>
<td>58</td>
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<tr>
<td>Index (impulses/sec mm Hg$^{-1}$)</td>
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<td>0.63</td>
<td>0.47</td>
<td>0.29</td>
<td>0.44</td>
<td>0.55</td>
<td>0.25</td>
<td>0.37</td>
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<tr>
<td>Historial †</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Media</td>
<td>+ to ++</td>
<td>++</td>
<td>+</td>
<td>+ to ++</td>
<td>++</td>
<td>+</td>
<td>++</td>
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<tr>
<td>Nerves</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

All values are means.

*Weeks after surgery are given in parentheses.

†The severity of the histological lesions is proportional to the number of plus signs.

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**Figure 2**

Graph showing the relationship between the impulse frequency and the aortic arch pressure of the baroreceptor fiber illustrated in Figure 3 during nonpulsatile perfusion of the aorta.

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FIGURE 3
Effects of altering the aortic arch pressure (nonpulsatile) on the impulse discharge in a baroreceptor fiber from the left aortic nerve of a rabbit with renal hypertension (mean arterial blood pressure 160 mm Hg, weight 2.5 kg). Isolated aortic arch preparation perfused with Krebs-Henseleit solution (37.5°C). A.A.P. = aortic arch pressure, E.N.G. = electroneurogram.

in pressure did not result in any increase in the impulse frequency compared with that in normal rabbits (Table 1). Thus the index at the point of inflection was lower than normal \( (P < 0.001) \) (Table 1). At the point of inflection, the majority of the fibers from rabbits with renal hypertension had an index of less than 0.6 impulses/sec mm Hg\(^{-1}\), but in the normal rabbits the majority had an index greater than 0.6 impulses/sec mm Hg\(^{-1}\).

Right Subclavian Baroreceptors.—In 15 fibers of five rabbits with hypertension, the threshold pressure and the pressure at the point of inflection were significantly higher than they were in 10 fibers of five normal rabbits that had a mean blood pressure ranging between 60 and 82 mm Hg \( (P < 0.05) \) (Table 1). However, the difference between the values in the two groups was less than the difference observed in the baroreceptors of the aortic arch (Table 1). Similarly the indexes of the threshold and the point of inflection were less in the rabbits with renal hypertension than in the normal rabbits. On the other hand, the gradient of the curves was relatively more depressed in the fibers studied from the right aortic nerve of the rabbits with renal hypertension \( (0.49 \pm 0.05 \text{ impulses/sec mm Hg}^{-1}) \) compared with the fibers from normal rabbits.

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than was the gradient of curves from the left aortic nerve (Table 1). However, the average blood pressure of the rabbits in the study of the right subclavian area was higher than that of the rabbits in the study of the aortic arch area, and they were hypertensive for a longer period of time (Table 1).

The types of fiber discharge patterns at their threshold pressure in the rabbits with renal hypertension were similar to those already described for the left aortic nerve. Type 1 discharge occurred in 13 fibers (87%) and type 2 in 2 fibers (13%) compared with values for the right aortic nerve in the control series of 70% type 1, 13% type 2, and 20% type 3.

Comparison of the Effects of Stepwise Increases and Decreases in Aortic Arch Pressure.—In the normal rabbit, the relationship between aortic blood pressure and baroreceptor impulse frequency is modified when a stepwise decrease in pressure is preceded by a stepwise increase in pressure (5). This phenomenon was explained on the basis of the altered mechanical properties of the arterial wall which occurred as a result of this maneuver. In view of the mechanical basis for this change, a similar procedure was performed on the rabbits with hypertension to determine if this phenomenon was more evident.

The changes in the activity of 19 fibers from six rabbits with hypertension (mean blood pressure 160.0 ± 11.3 mm Hg) were compared with the changes in the activity of 6 fibers from six normal rabbits (Table 3). Generally, there was a slightly wider separation of the curves of individual fibers from the rabbits with hypertension (Fig. 5) at all pressures compared with that for the normal rabbits. The separation diminished at the higher pressures and, in the normal rabbits, the curves were fused at pressures greater than 60 mm Hg above the original threshold pressure. By contrast, in the rabbits with hypertension there was still a significant (P < 0.02) separation of the curves at 100 mm Hg above the original threshold pressure (Table 3).

Relationship of the Change in Baroreceptor Activity to the Degree of Hypertension.—There was a direct relationship between the degree of hypertension observed in the experimental rabbits with renal hypertension and the amount of resetting of the aortic baroreceptors. Both the threshold pressures and the points of inflection were elevated above the corresponding values for normal rabbits (Fig. 6); the mean elevation of the threshold pressure was 1.21 ± 0.05 (SE) (r = 0.93, P < 0.001), and the equivalent value for the point of inflection was 1.39 ± 0.05 (SE) (r = 0.96, P < 0.001).

The depression of the gradient of the first part of the curves relating the baroreceptor impulse frequency to the aortic arch pressure was related to the degree of hypertension (Fig. 7) as well as to the number of weeks the rabbit had been hypertensive (Fig. 8). There was a closer correlation relationship between the time (gradient —17.8 ± 0.83 [SE] impulses/sec mm Hg⁻¹ week⁻¹; r = —0.91, P < 0.001) than between the actual degree

| TABLE 3 |
| --- | --- | --- |
| Comparison of the Difference (B — A) in the Relationship Between Aortic Arch Pressure and Baroreceptor Activity during a Stepwise Increase (A) and a Stepwise Decrease (B) in Pressure |

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>P</th>
<th>Renal hypertensive</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. rabbits</td>
<td>6</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. fibers</td>
<td>6</td>
<td>19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold pressure difference (mm Hg)</td>
<td>12.5 ± 8.9</td>
<td>&gt; 0.2</td>
<td>11.2 ± 5.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Threshold frequency difference (impulses/sec)</td>
<td>-2.3 ± 3.3</td>
<td>&gt; 0.5</td>
<td>-5.5 ± 4.3</td>
<td>&gt; 0.2</td>
</tr>
<tr>
<td>Frequency (impulses/sec)*</td>
<td>20 mm Hg</td>
<td>-12.4 ± 2.4</td>
<td>&lt; 0.01</td>
<td>-22.4 ± 5.3</td>
</tr>
<tr>
<td>40 mm Hg</td>
<td>-7.6 ± 2.6</td>
<td>&lt; 0.02</td>
<td>-9.6 ± 4.2</td>
<td>&lt; 0.02</td>
</tr>
<tr>
<td>60 mm Hg</td>
<td>-4.2 ± 3.2</td>
<td>&gt; 0.2</td>
<td>-8.7 ± 3.3</td>
<td>&gt; 0.02</td>
</tr>
<tr>
<td>80 mm Hg</td>
<td>-7.7 ± 2.7</td>
<td>&lt; 0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mm Hg</td>
<td>-8.0 ± 3.1</td>
<td>&lt; 0.02</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The values are means ± SE.

*Pressures given are pressures above the original threshold pressure.
Graph showing the relationship between the impulse frequency and the aortic arch pressure when the pressure was increased in steps (solid lines) and then reduced in steps (broken lines). The arrows indicate the direction of the change in pressure. Results from two fibers from a rabbit with renal hypertension (squares and triangles) and from one fiber from a normal rabbit (circles) are illustrated.

Pressure Volume Curves.—In six isolated perfused aortic arches from rabbits with renal hypertension with a mean blood pressure of 161.7 ± 1.23 mm Hg (range 125 to 200 mm Hg), eight pressure-volume curves were obtained and compared with eight pressure-volume curves in four normal rabbits with a mean blood pressure of 83.4 ± 1.3 mm Hg (range 80 to 85 mm Hg). The vascular volume of the preparation was larger in the rabbits with renal hypertension (0.86 ± 0.9 ml) than in the normal rabbits (0.7 ± 0.07 ml), suggesting that the aortic arch was dilated in the rabbits with renal hypertension because the two groups of rabbits were of a similar weight, 3.4 ± 0.23 and 3.2 ± 0.15 kg, respectively.

Since there was a difference in the volume of the preparations at zero pressure, the volume injected was expressed as a percent of the initial volume (Fig. 9). The pressure induced by a given percent increase in added volume was higher in the rabbits
Graph of the mean gradient of the first part of the curve relating baroreceptor impulse frequency to pressure plotted against the mean blood pressure of the rabbits with renal hypertension (solid circles) and the mean gradient ± se of the normal rabbits (open circle). The line is the calculated regression line weighted for the number of fibers included in each point.

Graph of the mean gradient of the first part of the curve relating baroreceptor impulse frequency to aortic pressure plotted against the postoperative week at which the terminal experiment was performed on the rabbits with renal hypertension (solid circles). The mean gradient ± se of the fibers from the normal rabbits has been plotted against zero time (open circle). The line is the calculated regression line weighted for the number of fibers included in each value.
with renal hypertension than in the normal rabbits. In both groups, the relationship was almost linear initially but, at added volumes greater than 200%, the pressure increased more sharply with volume in the group with renal hypertension. In the normal group the steepest part of the curve occurred at an added volume of 350% (Fig. 9). These results indicated that the distensibility of the aorta in rabbits with renal hypertension was less than that in normal rabbits, particularly at the higher pressure range.

MICROSCOPIC FINDINGS

Aortic Arch.—Histological studies were performed on 15 rabbits with renal hypertension. In all rabbits, there were typical hypertensive lesions scattered throughout the aortic arch including those areas known to contain baroreceptors.

The intima was thickened in places in all the rabbits but one which died within 3 weeks after the initial operation. Differential staining techniques, PTAH, which are specific for true elastin, did not show reduplication of the internal elastic lamina but provided evidence of pseudoelastin (10). The elastin was fragmented, wavy, and uneven in its staining properties.

The severity of the lesions appeared to depend on both the degree of the hypertension and the length of time the rabbits had been hypertensive. Thus, the most pronounced lesions were observed in the rabbits with the highest blood pressure and the longest period of hypertension; by contrast, the rabbit that died within 3 weeks of the initial operation had no intimal lesions.

The medial lesions consisted of areas of necrosis with increased amounts of collagen demonstrated by Masson and CI stains and of pseudoelastin and mucopolysaccharides demonstrated by CI and toluidine blue stains. The normal contour and the uniformity of their outline were absent.

In rabbits that had been hypertensive for periods of 20–109 weeks there was also evidence of calcification (Von Kossa’s stain). This observation was most profound in the rabbit that died 109 weeks postoperatively. Minimal lesions were observed in the rabbit that died within 3 weeks after nephrectomy, although there was some widening of the spaces between the elastic lamellae with an increase in the amount of mucopolysaccharides and most probably an increase in other substances from the plasma. Thus, the degree of the medial damage appeared to be related to the length of the hypertension and to the pressure to which the vessel had been exposed.

Nerve Endings.—Normal nerve endings in the aortic arch were observed in three normal rabbits and in the majority of the sections from the eight rabbits with hypertension, but in a few there were areas in which the nerve fibers appeared to be fragmented or the stained regions were diffuse and irregular in outline. There were also nerve endings in which the staining was patchy and suggested the presence of vesicles (Figs. 10 and 11). All these abnormalities indicated degeneration (11, 12).

There appeared to be marginally fewer stained nerve endings in the sections from the rabbits with hypertension than in the sections from the normal rabbits, but a quantitative assessment was difficult to make because the number of baroreceptor endings was related to the part of the aorta from which the sections were cut.

Discussion

There are noticeable differences in the relationship between the impulse frequency of single
baroreceptor units and the aortic arch pressure in rabbits with renal hypertension compared with that in normal rabbits. These differences include (1) an increase in the threshold pressure, (2) a reduction in the threshold index, (3) a diminution in the sensitivity of the baroreceptors as indicated by a...
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depressed gradient of the first part of the curve relating impulse frequency to pressure, (4) an increase in the pressure at the point of inflection, and (5) an impairment of function or a reduction in the number of baroreceptor units. A few degenerated endings were found histologically, as observed previously, in arterial baroreceptor areas in hypertensive man (11, 12).

These facts explain the previously observed changes in whole-nerve recordings in animals with renal hypertension (1–3): the diminished or the absent baroreceptor activity at normal levels of blood pressure, the reduced discharge at the resting level of blood pressure, and the occurrence of a phasic discharge at higher levels of pressure than occurs in the normal animal. This reduction in the baroreceptor activity would then cause less inhibition of the "vasomotor center" and help to contribute to the hypertension already produced by a renal cause.

The reduced sensitivity of the baroreceptors could be an important contribution to the lability of the blood pressure observed in the rabbits with hypertension and in patients with certain forms of hypertension, since a change in mean blood pressure produces a smaller change in individual baroreceptor activity and, hence, in compensatory vasomotor tone. This concept is supported by the fact that rabbits with denervated carotid sinuses and aortic arch have abnormally labile blood pressures (13). Moreover, the reduced sensitivity could explain, at least from the afferent side of the baroreflex pathway, the reduced blood pressure and cardiac responses following the injection of pressor substances in hypertensive patients (14).

MECHANISMS OF BARORECEPTOR RESETTING AND CHANGES OF SENSITIVITY

The observed changes in the characteristics of the baroreceptor discharge probably are due to alterations in the receptors themselves, to mechanical changes in the arterial wall in which the receptors lie, or to both. The large vessels of the perfused area from the rabbits with chronic renal hypertension had altered mechanical properties compared with those of normal rabbits, as demonstrated by their reduced distensibility and increased initial volume. These changes were greater than those observed in rabbits with acute hypertension (15) and were related to the length of time the rabbits had been hypertensive and to the severity of the histological lesions. Similarly, a high degree of correlation between the aortic wall tension and the increase in aortic weight, due mainly to an increase in the amount of elastin and collagen in the media, occurs in hypertension (16).

Changes in the mechanical properties of the arterial wall may alter the characteristics of the firing of the baroreceptors (5) or their reflex effects (17) in normal animals and animals with hypertension (3, this paper). Changes were evident in the present experiments because the sensitivity of the baroreceptors was reduced and the mean impulse frequency of the baroreceptor fibers was not increased and even diminished in the rabbits with hypertension, despite the elevated threshold pressure and the increased aortic diameter. The increase in the aortic diameter increases the arterial wall tension according to the law of Laplace and normally would be expected to increase the stretch acting on the baroreceptors and to increase their discharge and lower their threshold pressure. These findings indicate that there must be changes in the mechanical properties of the vessel wall resulting in an accentuation of the stress-relaxation phenomenon near the attachments of the baroreceptor nerve endings. A similar explanation accounts for the separation of the impulse frequency-pressure curves resulting from first raising and then lowering the aortic pressure and for the exaggeration of this response in the rabbits with hypertension.

In the present series, the baroreceptors had reset in all the rabbits; the minimum time was 7 weeks and the degree of the resetting was related to the degree of the hypertension. The reduction of the sensitivity of the baroreceptors to changes in pressure was directly related to the length of time that the rabbit had been hypertensive and, to a smaller extent, to the actual level of blood pressure to which the baroreceptors were exposed. The reduced sensitivity was explained by the increased stiffness of the hypertensive arteries as shown by the pressure-volume curves. This stiffness has a splinting action and therefore reduces the stretch applied to the baroreceptor endings for any increase of pressure compared with the stretch caused by that same pressure in normal rabbits. These changes in the baroreceptor fiber activity and the pressure-volume curves were demonstrated in an isolated perfused preparation and could not have been caused by the effects of hormones or of changes in sympathetic nerve activity occurring during the terminal experiment. The changes in fiber activity and the pressure-volume curves did not prevent the vessels from maintaining their alterations in water.
and electrolyte composition and in structure which resulted from the hypertension; these changes either followed the exposure to the high blood pressure per se (18) or were due to changes in sympathetic nerve activity (19) or altered secretions of hormones (angiotensin, prostaglandins, norepinephrine), which could all participate by affecting the smooth muscle tone of the aortic arch. The receptors could be directly affected by these factors because the baroreceptor nerve endings have intimate connections with the structures of the arterial wall (20). The large variation in the characteristics of baroreceptor fiber activity from normal to grossly abnormal must be related to the relationships of the fibers with these structures and to the varying and patchy lesions in the vessel walls of rabbits with hypertension. Although receptor fatigue has been suggested as a contributory cause of the changes in whole-nerve recordings (1, 3), it is probably not the cause in the present experiments since some fibers showed normal characteristics. Nevertheless, receptor damage must be considered to participate in baroreceptor malfunction.

**TIME COURSE OF BARORECEPTOR RESETTING**

In renal hypertension, the initial function of the baroreceptors is to oppose the rise in blood pressure because their resetting lags behind the hypertension (21), although it occurs within 5 days in the rabbit (3). This sequence suggests that baroreceptor dysfunction occurs as the result of the hypertension, rather than being the cause of the hypertension, and is probably partly the result of high pressure per se (18).

Early changes in water and electrolyte composition of the wall of the main arteries resulting from the high pressure would increase the stiffness of the vessels and contribute to the resetting (3), thereby reflexly enhancing the increased vascular resistance by a reduction of the inhibition of the vasomotor center. Removal of the precipitating cause of the hypertension at an early stage results in a decrease in blood pressure and an initial increase in heart rate (22), presumably partially due to diminished baroreceptor activity, and is followed by an increased excretion of sodium and water. Subsequently, there is a reduction of peripheral vascular resistance, which could be partially due to baroreceptor resetting towards the normal level.

Prolonged hypertension results in the formation of pathological lesions (16, this paper) in the arterial walls which further modify baroreceptor activity particularly in relation to the sensitivity of the receptors to changes in pressure (this paper). Furthermore, some receptors may suffer from irreparable damage from necrosis or from deficiency of nutrients resulting from the increase in the thickness of the wall. Consequently, there would be a further reduction of inhibition of the vasomotor center, and the hypertension would be maintained.

The longer the period of the hypertension the slower the blood pressure returns to normal on removal of the precipitating cause (23, 24). This observation is consistent with the effect of the resolution of the vascular lesions on the baroreceptor activity. However, there is as yet no information about the time course of the recovery of baroreceptor function at this stage or of its relationship to the gradual fall in arterial blood pressure.

It is evident that there are several mechanisms which could be responsible for the resetting of the baroreceptors and for the alterations in their sensitivity depending on the time course and the severity of the hypertension. In conclusion, the role of the resetting of the arterial baroreceptors in renal hypertension is seen not as a primary cause of the hypertension but as a contributory mechanism involved in the overall integrative response of the organism whereby the raised blood pressure helps to maintain a normal or near normal renal blood flow.

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JENNIFER E. ANGELL-JAMES

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