Arterial Baroreceptor Activity in Rabbits with Experimental Atherosclerosis

By Jennifer E. Angell-James

ABSTRACT

A total of 16 rabbits developed atherosclerosis after receiving a diet containing 1% cholesterol and 6% sunflower seed oil for up to 67 weeks. Their mean blood pressure rose from 85 to 114 mm Hg. The aortic arch region was isolated and perfused with Krebs-Henseleit solution, and the impulse activity of 70 single aortic and 8 right subclavian baroreceptor fibers was studied during step increases and decreases in perfusion pressure. The threshold pressure of the aortic baroreceptor fibers from the atherosclerotic rabbits was only slightly higher ($P > 0.4$) than that of 29 fibers from 17 normal rabbits, but the impulse frequency was less ($P < 0.02$). The gradient of the impulse frequency-pressure curves (0.73 impulses/sec mm Hg$^{-1}$), was significantly lower ($P < 0.01$) than normal (1.19 impulses/sec mm Hg$^{-1}$), as was the gradient of the curves from the right subclavian baroreceptor region. The curves resulting from first increasing and then decreasing the perfusion pressure were more separated in the atherosclerotic rabbits than they were in the normal rabbits. There was a correlation between the amount of the reduction in the sensitivity of the aortic baroreceptors and the length of time the rabbits had been on the lipemic diet ($r = 0.96$). The changes in the baroreceptor activity were associated with a reduction in the distensibility of the perfused area and with histological lesions in the baroreceptors and the arterial walls. The mild hypertension in the atherosclerotic rabbits could partly be accounted for by the reduction in aortic baroreceptor activity. Similar mechanisms might contribute to blood pressure anomalies in humans with atherosclerosis.

KEY WORDS: mild hypertension, aortic distensibility, aortic pathology, baroreceptor nerve endings, lipemic diet

Experimental renal hypertension in animals is associated with a reduction in carotid sinus and aortic arch baroreceptor activity (1-4). This reduction results from a decrease in the sensitivity of individual baroreceptors to changes in mean blood pressure (4) compared with the sensitivity of receptors in normal rabbits (5) and from an elevation in receptor threshold pressure (4). Furthermore, in hypertension resulting from calciferol intoxication, the sensitivity of the aortic arch baroreceptors is also diminished (6). In both of these forms of hypertension, the change in sensitivity of the baroreceptors is associated with a reduction in the distensibility of the aortic wall (4, 6, 7).

Hypertension is also associated with atherosclerosis, and attempts have been made at autopsies in humans to correlate the extent and the site of atherosclerotic lesions with the baroreceptor areas and the occurrence of hypertension (8). However, to my knowledge, recordings of single baroreceptor fiber activity in atherosclerotic animals or correlation of their activity with the level of blood pressure in this condition have not been made.

This paper describes the activity of the aortic arch baroreceptors, the changes in distensibility of the aortic wall, and the pathological lesions which are induced in rabbits with experimental atherosclerosis.

Methods

PRODUCTION OF ATHEROSCLEROSIS

A total of 16 New Zealand white rabbits, 3-4 months old, were fed a standard diet of rabbit pellets containing the following ingredients measured in parts by weight: oats 12, middlings 18, bran 40, fish meal (66% protein) 10, and grass meal (18% protein) 20. During the lipemic stages of the diet, the rabbits were given pellets (150 g/day) that had been embodied with 1% cholesterol and 6% sunflower seed oil. Four of these rabbits were fed the lipemic diet for 12 weeks, 4 rabbits were fed the lipemic diet for 17-31 weeks, and the remaining 8 rab-
bits received the diet in cycles of 12 weeks interspersed with 4 weeks on the ordinary diet. Five rabbits died before the terminal experiment, and the remaining 11 rabbits were allowed to recover for 1-6 weeks from the high-cholesterol diet before the terminal experiment.

Scrum cholesterol, alkaline phosphatase, sodium, potassium, calcium, and phosphate were measured during the control period before the introduction of the lipemic diet, after 10 weeks of the diet, and at the time of the terminal experiment (Table 1).

The blood pressure of the unanesthetized rabbits was measured before the commencement of the diet and at weekly intervals with a Grant-Rothschild capsule (9) placed over the central artery of the ear.

TERMINAL EXPERIMENT

At the time of the terminal experiment, the mean blood pressure of the 11 rabbits was measured with a Grant-Rothschild capsule; in 7 rabbits this measurement was compared with that obtained with an electromanometer connected to a polyethylene cannula inserted into the central artery of the ear under local anesthesia. The signals were recorded after suitable amplification on a multichannel ultraviolet light-recording oscillograph. Mean blood pressure was obtained electrically by passing the amplifier output through a single resistance-capacitance network with a time constant of 1 second. The mean blood pressure measured by the Grant-Rothschild capsule was 5.0 ± 2.7 mm Hg (range 0 to 20 mm Hg) higher than that measured in the central artery of the ear.

After commencement of the diet (33.9 ± 3.3 [SE] weeks, range 17 to 51 weeks), the 11 rabbits (3.4 ± 0.02 kg) were anesthetized with a solution of 25% urethane (1.6 ± 0.1 g/kg, iv, range 1.1 to 2.2 g/kg). A tracheostomy was performed, and a cannula was pushed down the right common carotid artery until its tip was in the aortic arch, heparin (1,000 IU/kg, ia) was administered. The blood pressure in the aortic arch was measured by connecting the cannula to the pressure transducer. The frequency response of the cathetermanometer system was determined by the method of Frank (10). The undamped natural frequency response of the system was greater than 70 cycles/sec; the degree of damping was 0.35. This frequency response gave an estimated amplitude distortion of less than 5% up to about 25 cycles/sec. The mean blood pressure measured by this method was 114.3 ± 3.2 mm Hg (range 98 to 130 mm Hg) and was higher than that measured with the

**Table 1**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Control</th>
<th>10th week</th>
<th>Experimental*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mEq/liter)</td>
<td>140.3 ± 1.4</td>
<td>139.0 ± 2.0</td>
<td>138.4 ± 1.3</td>
</tr>
<tr>
<td>Potassium (mEq/liter)</td>
<td>4.3 ± 0.05</td>
<td>4.1 ± 0.16</td>
<td>3.4 ± 0.46</td>
</tr>
<tr>
<td>Calcium (mg/100 ml)</td>
<td>13.4 ± 0.29</td>
<td>13.5 ± 0.15</td>
<td>12.0 ± 0.57</td>
</tr>
<tr>
<td>Phosphate (mg/100 ml)</td>
<td>6.1 ± 0.22</td>
<td>4.3 ± 0.29</td>
<td>2.7 ± 0.5</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU)</td>
<td>11.3 ± 1.1</td>
<td>8.2 ± 0.95</td>
<td>7.6 ± 1.9</td>
</tr>
<tr>
<td>Cholesterol (mg/100 ml)</td>
<td>70.6 ± 21.6</td>
<td>1875.6 ± 242.4</td>
<td>513.5 ± 122.5</td>
</tr>
</tbody>
</table>

*Experimental refers to the day of the final experiment.

The left or the right aortic arch was divided, and the baroreceptor activity in the whole nerve was recorded with saline-wick silver-silver chloride electrodes connected to a Tektronix 122 preamplifier and displayed on ultraviolet-sensitive paper after suitable amplification. Full details of the equipment and techniques have been described elsewhere (4, 5).

**ISOLATION AND PERFUSION OF THE AORTIC ARCH**

The aortic arch was isolated from the rest of the circulation as described previously (5) by ligating all the vessels arising from it (11); it was perfused with Krebs-Henseleit solution via a cannula in the side arm of the aortic cannula with its tip in the ascending aorta. The temperature of the perfusate was measured with a copper-constantan thermocouple and galvanometer and maintained constant at 37-39°C.

Single- and few-fiber recordings were made from the left and the right aortic nerves using saline-wick silver-silver chloride electrodes as described elsewhere (5).

**METHODS OF ANALYSIS OF RESULTS**

The method of analysis of the single-fiber activity in this paper was the same as it was in the previous studies (4, 5). The impulse frequency was plotted against the aortic arch pressure. The lowest pressure at which the baroreceptors discharged an impulse is called the threshold pressure. Above the threshold pressure, there was usually a linear relationship between the pressure and the impulse frequency, and the gradient of this part of the curve was measured. The point at which this linear relationship ceased is called the point of inflection. The threshold index and the index at the point of inflection were calculated by dividing the impulse frequency at these points by the pressure and expressing them as impulses/sec mm Hg⁻¹.

**STATISTICAL ANALYSIS**

The arithmetic means ± SE for a sample were calculated. To test the significance of the difference of the
means of two grouped values, $t$ was calculated as the
difference of the means divided by the standard error of
the difference of the means. The probability ($P$) corre-
sponding to the number of degrees of freedom ($N - n_1 + n_2 - 2$) was found from tables.
The relationships of baroreceptor activity to arterial
blood pressure and to the time between the commence-
ment of the lipemic diet and the terminal experiment
were estimated by calculating the regression line, which
was weighted to include the number of fibers in each
mean value.

**PRESSURE-VOLUME CURVES**
Pressure-volume curves for the aortic arch were
determined as described previously (4) by measuring
the peak pressure obtained in the perfused area after
the injection of a known volume of Krebs-Henseleit
solution at 37°C into the side arm of the aortic cannula.
The peak pressure was plotted against the injected
volume expressed as a percent of the original volume.

**HISTOLOGICAL STUDIES**
Histological sections were cut from the carotid
sinuses, the ascending and descending aorta, the liver,
the heart, the kidney, and the right subclavian artery.
The specimens were fixed in 10% formalin and
were embedded in wax. The sections were stained with
hematoxylin and eosin, Verhoeff and Van Gieson, Von
Kossa, toluidine blue, and Masson and Gomori stains.
Histochemical studies were made on the left carotid
sinus and the middle of the aortic arch with a modifica-
tion of the Koelle technique (12).

**Results**

**EFFECTS OF THE PRODUCTION OF ATHEROSCLEROSIS ON THE
BLOOD PRESSURE**

The blood pressure of 16 unanesthetized rabbits
rose from a control level of 85.6 ± 4.2 mm Hg
(range 70 to 115 mm Hg) to a peak level of
133.6 ± 3.2 mm Hg (range 115 to 170 mm Hg) 6-26
weeks (mean 14.3 ± 1.6 weeks) after the com-
mencement of the lipemic diet. Five rabbits died
from cholesterol intoxication or from complications
arising from their atherosclerosis. The remaining
11 rabbits survived until the terminal experiment
at which time they had a mean blood pressure of
114.3 ± 3.2 mm Hg. In 8 of these rabbits in which
technically successful measurements were made of
the phasic pressure, the mean systolic pressure was
138.5 ± 3.3 mm Hg, the mean diastolic pressure
was 92.3 ± 4.0 mm Hg, the mean pulse pressure
was 46.3 ± 3.3 mm Hg, and the heart rate was
252.8 ± 16.7 beats/min. Their blood pressure was
lower than it had been in the earlier part of the experi-
ment, but it was higher than the blood pressure
of normal rabbits of equivalent weight.

The blood pressure of seven unanesthetized
atherosclerotic rabbits was measured continuously
with the cannula in the central artery of the ear
during small spontaneous body movements. It was
slightly more labile than that of normal rabbits:
fluctuations from 0 to 25 mm Hg were observed
(mean 8.3 ± 3.4 mm Hg). The maximum fluctuation
in normal rabbits was 15 mm Hg (4).

**BARORECEPTOR ACTIVITY IN THE ISOLATED PERFUSED
AORTIC ARCH PREPARATION**
The physiological characteristics of the bar-
oreceptors of the aortic arch and the right subclavian artery were studied by recordings made
from the left and the right aortic nerves, respec-
tively. The results obtained from the nerves of the
atherosclerotic rabbits were compared with those
obtained previously from a group of normal control
rabbits using the same techniques (5).

**Aortic Arch Baroreceptors.**—The impulse ac-
tivity in 70 fibers from the left aortic nerve of 7
atherosclerotic rabbits with a mean blood pressure
of 114.7 ± 4.3 mm Hg (range 98 to 125 mm Hg)
was analyzed in records obtained by raising the
aortic arch pressure in steps from 0 mm Hg during
nonpulsatile perfusion. These results were com-
pared with those in 29 fibers from 17 normal rab-
bits (Table 2).

A recording from a typical single, active
baroreceptor fiber from the left aortic nerve of an
atherosclerotic rabbit is illustrated in Figure 1. The

![Figure 1](http://circres.ahajournals.org/)

**Effects of altering the aortic arch pressure (nonpulsatile) on the
impulse discharge in a baroreceptor fiber from the left aortic
nerve of an atherosclerotic rabbit (mean arterial blood pressure
at time of terminal experiment 100 mm Hg, weight 3.6 kg). Is-
olated aortic arch preparation perfused with Krebs-Henseleit
solution (37.5°C). A: Recorded at threshold pressure. B-D:
Recorded at successively higher pressures. A.A.P. = aortic arch
pressure, and E.N.G. = electroneurogram.
<table>
<thead>
<tr>
<th></th>
<th>Left aortic nerve</th>
<th>Right aortic nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Atherosclerotic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of rabbits</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>2.2 ± 0.12 (1.4-3.4)</td>
<td>3.4 ± 0.2 (2.3-4.2)</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>85</td>
<td>87.9 ± 6.5 (70-115)</td>
</tr>
<tr>
<td>Peak</td>
<td>129.3 ± 2.8 (120-140)</td>
<td>15.4 ± 2.5 (7-26)</td>
</tr>
<tr>
<td>Week</td>
<td>114.7 ± 4.3 (98-125)</td>
<td>31.9 ± 3.4 (17-41)</td>
</tr>
<tr>
<td>Threshold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of fibers</td>
<td>29</td>
<td>70</td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td>52.5 ± 5.5 (0-118)</td>
<td>57.9 ± 5.1 (0-200)</td>
</tr>
<tr>
<td>Frequency (impulses/sec)</td>
<td>34.1 ± 2.3 (12-59)</td>
<td>26.8 ± 2.0 (2-70)</td>
</tr>
<tr>
<td>Index (impulses/sec mm Hg(^{-1}))</td>
<td>2.89 ± 2.1 (0.13-59)</td>
<td>2.37 ± 0.68 (0.03-29)</td>
</tr>
<tr>
<td>Gradient (impulses/sec mm Hg(^{-1}))</td>
<td>1.19 ± 0.14 (0.28-2.85)</td>
<td>0.73 ± 0.07 (−0.43 to +2.77)</td>
</tr>
</tbody>
</table>

All values are means ± SE.  
The numbers in parentheses are ranges.
first record (A) shows the threshold pressure of that fiber. As the pressure was increased (B-D), the frequency of the impulse also increased. There was great variability in the relationship between the aortic arch pressure and the impulse frequency in the baroreceptor fibers from both normal and atherosclerotic rabbits. In general, as the pressure increased the relationship was linear initially and then the curve began to plateau at the point of inflection. Beyond this point the discharge decreased, increased, remained constant, or ceased altogether. Some fibers did not exhibit a point of inflection.

The mean threshold pressure of the left aortic baroreceptor fibers was elevated in three of the seven rabbits, was the same in one rabbit, and was lower in three rabbits; however, as a group the mean threshold pressure was not significantly higher (P > 0.4) than normal, although the range was much greater (Table 2). Some fibers fired at zero pressure, but others had a threshold pressure as high as 200 mm Hg (Table 2). However, there was a significant reduction in the frequency of the impulse at the threshold pressure of the atherosclerotic rabbits despite the higher pressure (P < 0.02).

The pattern of the discharge at the threshold varied. In nine fibers the impulse frequency was almost constant when the pressure was increased up to 100 mm Hg; it then increased with further increments in pressure. This phenomenon sometimes occurred in fibers from the normal rabbits, but the maximum range of pressure over which the impulse frequency remained constant was 40 mm Hg (threshold type 3) (5). In six other fibers from atherosclerotic rabbits the intermittent type of threshold was observed (type 2), but the majority had a critical threshold pressure (type 1).

The index of the threshold was not significantly different in the two groups (P > 0.7), but the majority of fibers from atherosclerotic rabbits had an index that was lower than that of normal rabbits.

The mean point of inflection was the same in atherosclerotic rabbits and normal rabbits (Table 2), but the highest pressure at this point was 225 mm Hg in the atherosclerotic rabbits and 158 mm Hg in the normal rabbits. Some of the atherosclerotic rabbits had fibers that showed biphasic curves relating aortic pressure to impulse frequency. After the first point of inflection the impulse frequency increased with pressure in a linear

**TABLE 3**

Data Obtained from Individual Rabbits with Atherosclerosis in which Recording Were Made from Baroreceptor Fibers of the Left Aortic Nerve

<table>
<thead>
<tr>
<th>Rabbit</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental wt (kg)</td>
<td>2.3</td>
<td>3.8</td>
<td>3.6</td>
<td>4.2</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>80</td>
<td>70</td>
<td>100</td>
<td>100</td>
<td>115</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Peak</td>
<td>130</td>
<td>130</td>
<td>130</td>
<td>135</td>
<td>145</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>Week</td>
<td>11</td>
<td>20</td>
<td>7</td>
<td>10</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>98</td>
<td>125</td>
<td>120</td>
<td>125</td>
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<td>120</td>
</tr>
<tr>
<td></td>
<td>Week</td>
<td>23</td>
<td>31</td>
<td>40</td>
<td>41</td>
<td>36</td>
<td>17</td>
</tr>
<tr>
<td>Threshold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of fibers</td>
<td>15</td>
<td>12</td>
<td>5</td>
<td>11</td>
<td>7</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Pressure (impulses/sec)</td>
<td>31.1</td>
<td>53.8</td>
<td>90</td>
<td>92.3</td>
<td>70</td>
<td>50.0</td>
<td>48.1</td>
</tr>
<tr>
<td>Frequency (impulses/sec mm Hg)</td>
<td>32.4</td>
<td>24.1</td>
<td>20.0</td>
<td>34.1</td>
<td>27.4</td>
<td>21.8</td>
<td>21.3</td>
</tr>
<tr>
<td>Index (impulses/sec mm Hg)</td>
<td>1.53</td>
<td>0.75</td>
<td>1.19</td>
<td>0.41</td>
<td>0.43</td>
<td>5.44</td>
<td>4.40</td>
</tr>
<tr>
<td>Gradient (impulses/sec mm Hg)</td>
<td>0.91</td>
<td>0.83</td>
<td>0.54</td>
<td>0.54</td>
<td>0.44</td>
<td>0.91</td>
<td>0.60</td>
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<tr>
<td>Point of inflection</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Number of fibers</td>
<td>11</td>
<td>8</td>
<td>4</td>
<td>11</td>
<td>6</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td>79.3</td>
<td>114.4</td>
<td>133.8</td>
<td>126.8</td>
<td>132.5</td>
<td>100.6</td>
<td>100.8</td>
</tr>
<tr>
<td>Frequency (impulses/sec)</td>
<td>73.2</td>
<td>47.6</td>
<td>35.3</td>
<td>50.2</td>
<td>56.2</td>
<td>53.1</td>
<td>45.0</td>
</tr>
<tr>
<td>Index (impulses/sec mm Hg)</td>
<td>0.93</td>
<td>0.44</td>
<td>0.36</td>
<td>0.41</td>
<td>0.47</td>
<td>0.55</td>
<td>0.45</td>
</tr>
<tr>
<td>Histology of the costa*</td>
<td></td>
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<tr>
<td>Intima</td>
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<td>+++</td>
<td>+++</td>
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<tr>
<td>Media</td>
<td>+</td>
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<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Calcification</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

All values are means.

*Severity of the lesions is proportional to the number of plus signs.
fashion and then inflected again at a higher pressure.

The frequency of impulses at the point of inflection and the index at the point of inflection were both significantly lower in the atherosclerotic rabbits ($P < 0.01$ and $P < 0.05$, respectively) (Table 2).

The most pronounced difference between the characteristics of the aortic baroreceptors in the atherosclerotic rabbits and those in the normal rabbits was in the gradient of the first part of the curves relating impulse frequency to aortic pressure. The gradient was $0.73 \pm 0.07$ impulses/sec mm Hg$^{-1}$ in the atherosclerotic rabbits compared with $1.19 \pm 0.14$ impulses/sec mm Hg$^{-1}$ in the normal rabbits ($P < 0.01$, Table 2). In some instances the discharge in the fibers from the atherosclerotic rabbits actually diminished as the pressure was raised. The results of each individual experiment including the histological findings are summarized in Table 3.

**Right Subclavian Baroreceptors.**—The activity of eight baroreceptor fibers from the right subclavian region of three atherosclerotic rabbits was compared with the activity of ten fibers from five normal rabbits (Table 2). In this small series of results the only significant difference between the two groups was the gradient of the curves relating the impulse frequency to the pressure ($P < 0.02$).

Thus the differences between the activity of the right subclavian baroreceptors in the normal and the atherosclerotic rabbits were less marked than the differences in the larger series of results on the aortic arch baroreceptors, although the depression of the gradient of the curves was the same ($0.46$ impulses/sec mm Hg$^{-1}$). However, the blood pressure of the rabbits used in the studies of the right subclavian receptors was lower than that of the rabbits used in the studies of aortic arch baroreceptors, although the former group of rabbits had been on the lipemic diet for a longer period of time (Table 2).

**Effects on Baroreceptor Activity of Raising and Lowering Aortic Arch Pressure in Steps.**—In six normal and six atherosclerotic rabbits, the effects on impulse activity of elevating aortic pressure in steps were compared with the effects of lowering it in steps. Figure 2 is a graphic representation of the mean values of the results of 6 fibers from normal rabbits and 23 fibers from atherosclerotic rabbits. In both groups the threshold pressure was higher after reducing the aortic pressure than it was initially, and the impulse frequency was less despite the higher pressure. The frequency of the impulses at any pressure on lowering the pressure was less than it had been initially on raising the pressure; the greatest differences occurred at the lower pressures (Table 4, Fig. 2). At the higher pressures the curves eventually overlapped. The separation of the curves was more marked in the atherosclerotic rabbits than it was in the normal rabbits and also extended over a greater pressure range (Table 4).

**Relationship between the Level of Blood Pressure and the Change in Baroreceptor Activity.**—Calculation of the regression lines indicated that there was no direct correlation between the level of arterial blood pressure in the atherosclerotic rabbits and the threshold pressure (gradient $0.38 \pm 0.08$ mm Hg/mm Hg, $r = 0.43$) or the point of inflection (gradient $0.24 \pm 0.11$ mm Hg/mm Hg).
TABLE 4
Comparison of the Difference (B - A) in the Effect on Baroreceptor Activity of Reducing the Aortic Arch Pressure in Steps (B) after Previously Raising the Pressure in Steps (A) in Normal and Atherosclerotic Rabbits

<table>
<thead>
<tr>
<th>Number of rabbits</th>
<th>Normal</th>
<th>P</th>
<th>Atherosclerotic</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Number of fibers</td>
<td>85.0</td>
<td>&gt;0.2</td>
<td>113.0 ± 4.6</td>
<td>&gt;0.3</td>
</tr>
<tr>
<td>Threshold pressure difference (mm Hg)</td>
<td>12.5 ± 8.9</td>
<td>&gt;0.5</td>
<td>8.5 ± 4.5</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Threshold frequency difference (impulses/sec)</td>
<td>-2.3 ± 3.3</td>
<td>&gt;0.2</td>
<td>-11.1 ± 4.4</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Frequency (impulses/sec)* 20 mm Hg</td>
<td>-12.4 ± 2.4</td>
<td>&lt;0.01</td>
<td>-19.1 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>40 mm Hg</td>
<td>-7.0 ± 2.6</td>
<td>&lt;0.02</td>
<td>-11.5 ± 2.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>60 mm Hg</td>
<td>-4.2 ± 3.2</td>
<td>&gt;0.2</td>
<td>-8.1 ± 2.9</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>80 mm Hg</td>
<td>-6.2 ± 2.7</td>
<td>&gt;0.2</td>
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<td></td>
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</tbody>
</table>

All values are means ± SE.

*Pressures given are pressures above the original threshold.

Hg/mm Hg, r = 0.25) of the baroreceptor fibers from the aortic arch region. But there was a relationship between the gradient of the curves relating aortic arch pressure to baroreceptor impulse frequency (gradient 44.5 ± 4.5 mm Hg/impulse sec⁻¹ mm Hg⁻¹, r = 0.71) and arterial blood pressure. The gradient was lowest in the rabbit with the highest blood pressure.

The mean threshold pressure of the fibers studied in each atherosclerotic rabbit and the time between the commencement of the lipemic diet and the terminal experiment were not directly related (gradient 0.41 ± 0.08 weeks/mm Hg, r = 0.48), although the three rabbits that had been on the diet for the longest period of time had higher mean threshold pressures. However, there was a very close correlation between the gradient and the time on the diet (gradient 57.1 ± 1.73 weeks/impulse sec⁻¹ mm Hg⁻¹, r = 0.96) (Fig. 3). The rabbit that had been on the diet for the shortest period of time (17 weeks) had the most sensitive baroreceptors despite a relatively high mean arterial blood pressure of 120 mm Hg; however, the rabbits with the least sensitive baroreceptors had been on the diet for the longest period of time (Fig. 3).

Pressure-Volume Curves.—In six atherosclerotic rabbits with a mean weight of 3.5 ± 0.16 kg and a mean blood pressure of 115.0 ± 3.7 mm Hg (range 100 to 125 mm Hg), nine pressure-volume curves for the aortic arch region were obtained. These results were compared with eight pressure-volume curves from four normal rabbits of equivalent weight (3.2 ± 0.15 kg) with a mean blood pressure of 83.4 ± 1.3 mm Hg (range 80 to 85 mm Hg) (Fig. 4). The volume of the region under study was larger in the atherosclerotic rabbits (1.18 ± 1.9 ml, range 1 to 1.5 ml) than it was in normal rabbits (0.7 ± 0.07 ml), indicating that the atherosclerotic vessels were dilated. This comparison was confirmed by direct observation. There was little difference between the two curves at the lower pressures when small volumes of fluid were injected, but as the volume injected increased so did the difference between the curves. The pressure rose steeply in the aortas of atherosclerotic rabbits when the volume was increased by 300%, but the pressure only began to rise slowly in the normal vessels when the volume was increased by 350%. These results indicate that the atherosclerotic...
vessels were stiffer than the normal vessels at the higher pressures.

HISTOLOGY

Aortic Arch.—Histological studies were carried out on the aortic arches of 15 atherosclerotic rabbits 13–49 weeks after the commencement of the diet. In all rabbits there were demonstrable fibrous lesions in the vicinity of the baroreceptors and in other locations (Table 5). The lesions were similar to those described by other authors; they consisted of atheromatous plaques involving the intima with slight intimal-medial involvement. In some rabbits, complicated lesions with gruel formation and calcification were also present.

There were intimal plaques with lipid-filled foam cells, crystals of cholesterol, and early calcification (granules) at the base of intimal lesions, as shown in the Von Kossa-stained sections (Fig. 5).

Collagen was present in the subendothelial region and in the intimal-medial region and was much more evident in the rabbits that had been on the intermittent lipemic diet than it was in those that had been on the continuous lipemic diet followed by a recovery period before the terminal experiment. One rabbit (no. 1, Table 3) had only one small lesion involving the intima and a blood pressure that was within normal limits.

There were foam cells in the media. The elastic laminas nearest the intima were ruptured and frayed in some regions behind the intimal lesions. The disruption of the elastic laminas (shown in Gomori-stained slides, Fig. 5) was more pronounced in those rabbits on the intermittent lipemic diet. In one rabbit (no. 7, Table 3) the lesions were so extensive that they caused the development of an aneurysm. In all sections there was separation of the intimal-medial layers of elastic laminas, and in some sections there was evidence of early calcification. The involvement of the media

<table>
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<tr>
<th>Rabbit number</th>
<th>Mean blood pressure (mm Hg)</th>
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<th>Media</th>
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<td>40</td>
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</table>

Severity of the lesions is related to the number of plus signs.

*Presence of calcium.
BARORECEPTORS AND ATHEROSCLEROSIS

Photomicrographs of sections from the aortic arch of atherosclerotic rabbits. A: Rabbit no. 14 42 weeks after the commencement of lipemic diet when the arterial blood pressure was 115 mm Hg; Gomori stain for elastin. B: Rabbit no. 12 20 weeks after the commencement of the diet; Von Kossa’s stain for carbonate. Bars represent 100 μm.

was most marked in those rabbits whose baroreceptor activity showed the lowest gradients for the curves relating baroreceptor activity to aortic arch pressure. The two rabbits (nos. 1 and 6, Table 3) that had the mildest medial lesions and the most normal gradients of baroreceptor activity had been on the lipemic diet for the shortest period of time, although in one of these rabbits (no. 6) the intimal atheroma formed a complete lesion surrounding the surface of the aorta.

Baroreceptor nerve endings were stained for acetylcholinesterase with a modification of the Kölle technique. Positive stains with identifiable nerve endings were found in sections from four rabbits. Degenerate endings were also seen in several sections. In one rabbit (no. 2, Table 3) normal baroreceptor nerve endings were seen in parts of the aortic wall that had the least atheroma (Fig. 3) and abnormal endings, showing vacuolation and degeneration, were seen in a region where there were gross architectural abnormalities (Fig. 6). The number of normally stained nerve endings was slightly fewer than the corresponding number in similar sections from normal rabbits.

Heart.—All the rabbits fed the lipemic diet had atheroma of the coronary arteries or their smaller branches, and four rabbits had evidence of healed cardiac infarcts.

Kidneys.—Serial sections of the kidneys of the atheromatous rabbits were not cut, but in those sections that were studied there was evidence of atheromatous changes in the renal arteries of 12 of the rabbits (Table 5). These lesions ranged from small localized areas of intimal fibrosis and proliferation to larger areas of atheroma containing deposits of calcium which encroached on the lumen of the vessels.

Discussion

BARORECEPTOR ACTIVITY AND PRESSURE

The modifications in baroreceptor activity found in atherosclerotic rabbits resulted in diminished activity at any given pressure in comparison with activity in normal rabbits (5) in both the individual fibers and the whole nerves. The alteration in the activity of single units was not so marked as that
Baroreceptor activity and distensibility

The reduction in distensibility of the athero...
sclerotic vessels at levels of pressure found in the treated rabbits agrees with previous studies (13). Baroreceptors are stretch receptors whose activity is related mainly to the mechanical properties of the wall in which they are situated (3, 14, 15). Artificially restricting expansion of the carotid sinus prevents baroreceptor reflex control of the circulation in response to induced changes in carotid sinus pressure (16) and, on a long-term basis, causes chronic hypertension (17). Thus, the diminished distensibility of the wall in the present experiments resulted in a reduction in aortic baroreceptor sensitivity to changes in pressure. Moreover, the three atherosclerotic rabbits with the least distensible aortas had the least sensitive baroreceptors as judged by the gradient of the impulse frequency-aortic pressure curves.

The results of the relationship between the gradient of the first part of the impulse frequency-pressure curve and the distensibility of the aorta in the present experiments may be compared with those obtained in calciferol-treated rabbits (6) and renal hypertensive rabbits (4). The greatest reduction in baroreceptor sensitivity was associated with the least distensible aortas in the calciferol-treated rabbits, and the least change in baroreceptor sensitivity was associated with the most distensible aortas in the atherosclerotic rabbits. The renal hypertensive group of rabbits fell between the two other groups in so far as baroreceptor sensitivity and aortic distensibility are concerned.

The increased separation of the impulse frequency-pressure curves which occurred during the production of hysteresis in the atherosclerotic rabbits and the renal hypertensive rabbits (4) can also be explained by a change in the mechanical properties of the arterial walls, because the relative amounts of collagen, elastic tissue, smooth muscle, and calcium in the walls of arteries alter their viscoelastic properties. The increase in the collagen content and the destruction of the elastic laminas in the atherosclerotic rabbits cause a wider separation of the pressure-volume curves when the pressure is first increased and then decreased in steps. These changes in the viscoelastic properties should also modify the baroreceptor activity because of the close association between the nerve endings and the different components of the arterial wall.

HISTOLOGY AND BLOOD PRESSURE

All the rabbits fed a high-cholesterol diet developed atherosclerosis as observed originally by Anitschkow (18). If, as in the present experiments, this diet is followed by a recovery period or is administered intermittently, then lesions are produced which are not unlike those seen in human atherosclerosis (19–21). The extent of arterial involvement depends on the duration of the diet and the method of feeding the diet (22, 23).

Although there was no direct relationship between the degree of hypertension and the extent of the histological lesions involving the baroreceptor areas in the present experiments or in human autopsies (8), there was nevertheless medial involvement of the elastic laminas which was related to the length of time the rabbits had been on the lipemic diet. This involvement was directly related to the reduction in the sensitivity of the baroreceptors. However, there is also evidence that hypertension per se is partly responsible for the extent of the atheroma formation (24–26).

The production of atherosclerotic lesions and the elevation in the mean blood pressure occurred after 4 weeks of treatment, which is about the time required for lipid-filled foam cells to accumulate in the intima and the media of the arterial walls (22). However, connective tissue proliferation occurred only after 8 weeks on the lipemic diet. Presumably, this change combined with the degeneration of the inner layers of the elastic laminas was responsible for the alteration in the pressure-volume curves and the reduction in the sensitivity of the baroreceptors. The calcification at the base of the atherosclerotic lesions must further modify both the local characteristics of the arterial wall and the functional activity of the baroreceptors in that region. The possibility that factors other than the gross histological changes observed in the baroreceptors from normal to grossly abnormal in relation to the type of threshold, the pressure at the threshold, and the shape of the impulse frequency-pressure curves.

The predilection of the atheromatous plaques for sites at the origin and the division of arteries is
well known (27–29), and more recently a higher incidence of atheroma involving the region of the bifurcation of the common carotid artery more than the other parts of the common carotid artery has been found in humans (30). Changes of laminar flow occur in this region. In the present experiments atherosclerotic lesions were observed at similar sites, namely, the carotid sinuses, the subclavian-carotid angle, the aortic arch, and the origin of the superior thyroid artery from the common carotid artery. All these sites are areas in which baroreceptors are situated (15).

The population of baroreceptors is probably reduced as indicated by the degeneration of the nerve endings in the regions of atheromatous lesions in the aortic arch. This view is supported by the finding that in atherosclerotic rabbits the activity in whole aortic nerve recordings was less than that in normal rabbits with equivalent blood pressures (unpublished observations). However, normal baroreceptor nerve endings were found in neighboring regions of the sections in which pathological endings were seen, but they were situated in areas with less gross lesions. Thus degeneration of the receptors may be at least in part due to lack of nutrients rather than to high blood pressure alone. Abraham (31) found degenerating baroreceptor nerve endings in sections taken from human arteries with bifurcation of the common carotid artery. All these sites are areas in which baroreceptors are situated (15).

All of this evidence suggests that the mild degree of hypertension seen in atherosclerotic rabbits may be reflexly engendered through an increase in sympathetic nerve activity and hence in peripheral vascular resistance, resulting from a reduced baroreceptor population, reduced baroreceptor activity, and reduced distensibility of the aortic arch wall, which in turn leads to a reduction in baroreceptor sensitivity. Furthermore, the reduction in baroreceptor sensitivity accounts for the increased lability of the blood pressure found in the atherosclerotic rabbits. This increased lability occurs in other conditions in which the baroreceptor activity is reduced and appears to be directly related to the amount of reduction in their sensitivity (32). A reduction in baroreflex sensitivity has been observed in aging humans (33) who have less distensible aortas (34) and probably atherosclerosis. A similar explanation may account for the hypertension and the increased lability of blood pressure occurring in patients with extensive atheroma involving the arterial baroreceptor areas. Patients who undergo endarterectomy of the carotid sinus region for complications arising from atheroma might exhibit changes in their blood pressure-regulating mechanism in the postoperative period through an alteration in the viscoelastic properties of the vessel wall resulting from the removal of the atheromatous plaques.

However, there are other mechanisms by which the blood pressure could be increased: increased cardiac output, generalized narrowing of the resistance vessels through pathological changes, and increased secretion of renin resulting from atherosclerosis of the renal vessels. The latter mechanism also participates in the etiology of the hypertension in these rabbits because several rabbits had atheroma of these vessels. The cardiac output was not measured, but the rabbits all had normal blood pressure and the cardiac output in these rabbits because several rabbits had atheroma involving the arterial baroreceptor areas.

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References

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Arterial Baroreceptor Activity in Rabbits with Experimental Atherosclerosis

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