Carotid Sinus Baroreceptor Reflex Control of the Circulation in Medial Sclerotic and Renal Hypertensive Rabbits and Its Modification by the Aortic Baroreceptors

Jennifer E. Angell-James and M.J. George

SUMMARY We studied the reflex control of blood pressure, heart rate, and hindlimb vascular resistance by the carotid sinus baroreceptors in normal (N), experimental renal hypertensive (RH, one kidney renal wrap model), and medial sclerotic (MS) rabbits under urethane anaesthesia using an isolated perfused carotid sinus preparation and auto-perfused hindlimb. The contralateral carotid sinus was denervated. Compared to N rabbits, the blood pressure and hindlimb vascular resistance of RH and MS rabbits were significantly elevated at all carotid sinus pressures 15 weeks after inducing the disease process. The maximum gains of the curves relating carotid sinus pressure to vascular resistance were significantly elevated in the MS and RH rabbits, but those relating carotid sinus pressure to heart rate were significantly reduced. The changes were greatest in the RH group in which the responses also were set to a higher carotid sinus pressure. In the three groups, division of the aortic nerves produced different changes in the sigmoid curves relating carotid sinus pressure to heart rate, blood pressure, and vascular resistance. There was a linear relationship between blood pressure and basal vascular resistance (correlation coefficient 0.88). Circ Res 47: 890-901, 1980

THβ activity of the carotid sinus and aortic arch baroreceptors is modified by experimental renal hypertension (McCubbin et al., 1956; Kezdi, 1962; Kreiger and Marsillan, 1966; Aars, 1968; Angell-James, 1973), atherosclerosis (Angell-James, 1974a), and vitamin D-induced medial sclerosis (Angell-James, 1974b). The threshold pressure for the commencement of baroreceptor activity is increased in studies on both whole nerve (McCubbin et al., 1956; Kezdi, 1962; Kreiger and Marsillan, 1966; Aars, 1968) and single fibers in renal hypertensive and atherosclerotic animals (Angell-James 1973, 1974a). The threshold pressures of single baroreceptor fibers in medial sclerotic rabbits is reduced (Angell-James, 1974b), and all studies report a reduced sensitivity of the baroreceptors to changes of blood pressure above their threshold pressure. These changes may be expected to produce a modification of arterial baroreceptors reflex control of the circulation in these conditions. Previous reports (Bouckaert et al., 1937; Goldblatt et al., 1940; Conway, 1955; McCubbin et al., 1956; Alexander and DeCuir, 1966) indicate that baroreceptor reflexes are active in the regulation of acute changes of blood pressure in hypertensive animals. Other evidence has indicated, however, that baroreflex control of the P-P or R-R interval induced by pressor drugs is reduced in hypertension (Bristow et al., 1969; Gribbin et al., 1971; Angell-James and George, 1980) and it is associated with increased pressor responses to infused vasoconstrictor substances (Brown and Maegraith, 1941; Doyle, 1968).

In this study we investigated the carotid sinus baroreceptor reflex control of blood pressure, heart rate, and hindlimb vascular resistance in rabbits with experimental renal hypertension and vitamin D-induced medial sclerosis. In normal animals, carotid sinus baroreceptor reflexes are known to be modified by the concomitant stimulation of aortic baroreceptors. The extent of this modification was
ascertained by investigating the carotid sinus reflex control of the circulation before and after division of the aortic nerves.

Methods

New Zealand White rabbits, 3–9 months of age, were caged individually and fed a standard pellet diet (SG18 E; Dixon and Sons (Ware) Ltd) with unrestricted water.

Induction of Cardiovascular Disease and Hypertension

Medial Sclerosis

Medial sclerosis was induced by the administration of 50,000 IU Calciferol and 1 g calcium lactate in 2 ml of water given by stomach tube for 10 days (Angell-James, 1974b).

Renal Hypertension

Renal hypertension was induced by unilateral renal encapsulation with polyethylene (Angell-James, 1973) and contralateral nephrectomy under sodium pentobarbital anesthesia [Nembutal, Abbott Laboratories Ltd: 40 ± 2.7 mg/kg, iv (mean ± SE)].

Mean blood pressure was measured prior to renal wrapping or calciferol administration and before the terminal experiment by direct cannulation of the central ear artery under local anesthesia (2% lidocaine solution; Willows and Frances Ltd).

The Terminal Experiment

Some weeks (Table 1) after induction of medial sclerosis and renal hypertension, the rabbits were anesthetized with urethane (ethyl carbamate, 25% solution; May and Baker Corp., 1.7 g/kg, iv). One carotid sinus was isolated vascularly and perfused with blood from the cannulated common carotid artery; the other was denervated. During a test, the nonpulsatile pressure in the carotid sinus was raised in steps from 60 to 240 mm Hg by means of a pressure bottle. Body temperature (rectal) and carotid sinus temperature were monitored and maintained at 37°C, the latter was monitored by a thermocouple placed in the occipital artery. The aortic nerve on each side was identified at the junction of the superior laryngeal nerve with the vagus nerve. The blood was rendered incoagulable by heparin (Weddel Pharm. Ltd.), 1000 IU/kg, iv.

Pressure Recording

Mean carotid sinus pressure, phasic femoral artery pressure, and mean hindlimb perfusion pressure were recorded using electromanometers (Bell and Howell, type 4) and their outputs were amplified and displayed on a Devices M19 pen recorder. The flat response ± 5% of the femoral artery catheter-manometer system was better than 30 Hz (Frank, 1903). Mean femoral artery pressure and heart rate were derived from the pulsatile femoral artery trace.

Hindlimb vascular resistance was obtained by recording limb perfusion pressure at a constant flow

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of Blood Pressure and Heart Rate in Normal, Medial Sclerotic, and Renal Hypertensive Rabbits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>Number of rabbits</td>
<td>12</td>
</tr>
<tr>
<td>Unanesthetized: Disease process (wks)</td>
<td>15.2 ± 1.4</td>
</tr>
<tr>
<td>Weight (kg):</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Terminal experiment</td>
<td>3.05 ± 0.5</td>
</tr>
<tr>
<td>Mean ear artery pressure (mm Hg):</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>83.0 ± 1.1</td>
</tr>
<tr>
<td>Terminal experiment</td>
<td>96.0 ± 5.2 (P &lt; 0.05)</td>
</tr>
<tr>
<td>Anesthetized: Femoral artery pressure (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>88.0 ± 3.0 (range 73-111)</td>
</tr>
<tr>
<td>Systolic</td>
<td>117.0 ± 4.5 (range 102-147)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>81.0 ± 3.4 (range 61-93)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>251.0 ± 11.0 (range 222-309)</td>
</tr>
</tbody>
</table>

Values are the means ± SEM.

* Significance at the 5% level according to Scheffe's significance test and a one-way analysis of variance.
perfusion provided by a roller pump (Watson-Marlow Ltd.). Basal vascular resistance in the hindlimb devoid of sympathetic nervous influence was assessed after the administration of hexamethonium bromide (Sigma Pharmaceuticals Ltd) in a dose (usually 10 mg/kg) sufficient to block any change of vascular resistance by the elevation of carotid sinus pressure to 200 mm Hg. Samples of arterial blood were withdrawn anaerobically and analyzed for \( P_{O_2} \), \( P_{CO_2} \), and \( pH \) using a calibrated electrode system [model 413, Instrument Laboratories (UK) Ltd.].

**Statistical Methods**

All group values quoted are expressed as the mean plus or minus the standard error of the mean. Tests of significance between groups of data were performed on independent parametric samples according to a two-tailed \( t \)-test. The difference of two means of grouped values were calculated as the difference of the means divided by the standard error of the difference of the means, with \( P \) corresponding to the degrees of freedom \( N - n_1 + n_2 - 2 \). A comparison of values for blood pressure and heart rate of the three groups of rabbits (Table 1) were analyzed according to one way analysis of variance (ANOVA) and the significance was determined by Scheffe's test.

**Analysis of Carotid Sinus Baroreceptor Stimulus-Response Curves**

There is a sigmoid relationship between carotid sinus pressure and blood pressure, heart rate, and vascular resistance (Koch, 1931; this paper). The simplest mathematical models that could be fitted to such curves are third or fourth order polynomial functions, although the true function describing a sigmoid curve of this kind is a transcendental function of considerable complexity. In this study the best fit third or fourth order polynomial was determined for the data of each curve using a computer based least squares regression analysis derived from Forsythe's method using orthogonal polynomials (Snedecor and Cochran, 1967). The maximum slope of each of these curves was obtained as an index for the maximum reflex gain of the carotid sinus baroreceptor reflex, and its position, with respect to carotid sinus pressure, was identified.

**Results**

Compared with their normal control values, the blood pressure in the unanesthetized medial sclerotic rabbits was significantly elevated by 13 mm Hg \( (P < 0.05) \) and that of the renal hypertensive group by 47 mm Hg \( (P < 0.01) \) (Table 1). The values for blood pressure after urethane anesthesia were presented in Table 1. Analysis of the arterial blood indicated that initial values for \( P_{O_2} \) were greater than 100 mm Hg, the \( P_{CO_2} \) 25-27 mm Hg, and \( pH \) 7.35-7.38.

**Carotid Sinus Baroreceptor Reflex Control of Cardiovascular System**

In these experiments the carotid sinus reflex was studied in rabbits in which the other arterial baroreceptor areas were denervated by division of the contralateral carotid sinus nerve and both aortic nerves.

**Blood Pressure**

Typical recordings of blood pressure obtained by stepwise increases of carotid sinus pressure in a medial sclerotic and a renal hypertensive rabbit are illustrated in Figure 1. The curves relating carotid sinus pressure to mean arterial blood pressure were sigmoid in shape, and Figure 2 shows a comparison of the averaged results from 12 normal, 20 medial sclerotic, and 8 renal hypertensive animals. The curves were shifted to higher blood pressure levels in both the medial sclerotic and renal hypertensive rabbits (Fig. 2). In the normal rabbits, a change of

![Figure 1: Recordings of blood pressure (BP) and hindlimb perfusion pressure (HLP) at different carotid sinus pressures (CSP) in a medial sclerotic rabbit (MS, wt. 4.4 kg; mean BP, 97 mm Hg) and a renal hypertensive rabbit (RH, wt. 3.4 kg; mean BP, 127 mm Hg) after section of the aortic nerves.](http://circres.ahajournals.org/)

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carotid sinus pressure from 60 mm Hg to 200 mm Hg resulted in a fall of blood pressure of 55 mm Hg. A similar change of carotid sinus pressure produced a greater reduction of blood pressure in the medial sclerotic (67 mm Hg), and the greatest change of 71 mm Hg was recorded in the renal hypertensive rabbits.

In the renal hypertensive group (Fig. 2) the gain of the relationship between carotid sinus pressure and blood pressure was less than that of the normal and medial sclerotic rabbits at carotid sinus pressures below 120 mm Hg, but greater above this pressure (Fig. 2). The maximum gain was slightly reduced in the RH and MS rabbits (Table 2; \( P > 0.1 \)) and occurred at a higher carotid sinus pressure in the RH than in the normal and medial sclerotic rabbits.

Inspection of Figures 2 and 3 indicates that, in N and MS rabbits, raising the carotid sinus pressure by 40 mm Hg produced the greatest change of blood pressure around their normal blood pressure of 80 to 120 mm Hg; in the RH rabbits, however, the same change in carotid sinus pressure had a maximum effect at the higher blood pressures of 120 to 160 mm Hg, which is normal for the group. Thus, at low carotid sinus pressures the normal and medial sclerotic animals have a better control of their blood pressure than the renal hypertensive, whereas at the middle and higher ranges of pressures the renal hypertensives are better able to control their blood pressure than either the medial sclerotic or the normal rabbits.

Heart Rate

A direct comparison of the curves relating carotid sinus pressure and heart rate in the three groups of rabbits is shown in Figure 4. The relationship between carotid sinus pressure and heart rate was altered in such a way that in renal hypertensive rabbits the heart rate was faster at all carotid sinus pressures above 90 mm Hg. In the medial sclerotic group, the heart rate was slower below 120 mm Hg and higher above this pressure. The range of control of heart rate was also altered: an increase of carotid sinus pressure from 60 to 200 mm Hg produced a decrease of heart rate of 60% of the normal value in the medial sclerotic group and 38% of normal in the renal hypertensive group.

The carotid sinus pressure at which maximum gain occurred was, in the normal rabbits, approximately 100 mm Hg; in the medial sclerotic, 105 mm Hg; and in the renal hypertensive, 160 mm Hg. They were therefore all above the mean blood pressure of the group of animals being studied (Table 1). There was a significant reduction of the maximum gain of the heart rate in both the renal hypertensive and medial sclerotic groups \((P < 0.05)\), the difference being greatest in the former. However, above a pressure of 160 mm Hg the carotid sinus baroreceptor control of heart rate was greatest.
in the renal hypertensive rabbits (Figs. 3 and 4).

Altering the carotid sinus pressure by 40 mm Hg in the vicinity of the mean blood pressure of each group produced only half of the change of heart rate in the pathological groups compared to normal. At the highest range of pressures (160–200 mm Hg), the control of heart rate was equivalent in each group (Fig. 3).

Vascular Resistance

The typical response is illustrated by Figure 1. As with the other variables, the relationship between carotid sinus pressure and hindlimb vascular resistance was sigmoid in all three groups of rabbits (Fig. 5). The vascular resistance was reset to a higher level at any given carotid sinus pressure in the medial sclerotic and renal hypertensive groups, being highest in the latter group.

A change of carotid sinus pressure from 60 to 200
mm Hg produced a greater reduction of vascular resistance in the renal hypertensive and medial sclerotic groups than in the normal group. Raising the carotid sinus pressure from 80 to 120 mm Hg, which was the range of blood pressures of the normotensive rabbits, produced similar and maximum decreases in vascular resistance in both normotensive and hypertensive rabbits (Fig. 3). In the higher range of the blood pressure of the hypertensive rabbits (120 to 160 mm Hg), the same rise in carotid sinus pressure resulted in a change of vascular resistance in the RH rabbits which was more than double that in the normotensive ones at the same range of blood pressure (Fig. 3).

The maximum gain was significantly elevated in both the medial sclerotic and hypertensive groups \((P < 0.05)\), being greatest in the latter at a pressure above 120 mm Hg, and occurred at carotid sinus pressures of 100, 110, and 140 mm Hg in the normal, medial sclerotic, and renal hypertensive groups, respectively (Table 2; Fig. 5).

**Basal Vascular Resistance**

Vascular resistance determined after administration of hexamethonium was elevated in both the medial sclerotic and renal hypertensive groups to 145% and 212% of the control group, respectively (Fig. 5). There was a significant correlation between the mean arterial blood pressure measured from the femoral artery in the anesthetized rabbits at the commencement of the experiment and the basal vascular resistance of all animals included in these groups \((r = 0.88, P < 0.01)\) (Fig. 6).

**Modification of Carotid Sinus Reflex by Aortic Baroreceptors**

The role of the aortic baroreceptors in compensating the reflex cardiovascular response elicited by alterations of carotid sinus pressure was examined in rabbits before and after cutting the aortic nerves.

**Blood Pressure**

In normal rabbits, division of the aortic nerves increased the blood pressure at low carotid sinus pressures (CSP) and diminished the pressure at higher carotid sinus pressures (Fig. 7). The maximum gain before aortic nerve section was 0.38 mm Hg/mm Hg CSP and occurred at a carotid sinus pressure of 115 mm Hg, and this increased to 0.78 mm Hg/mm Hg CSP at 101 mm Hg after division \((P < 0.01)\) (Table 2).

In the medial sclerotic group of rabbits, division of the aortic nerve elevated the curve relating blood pressure to carotid sinus pressure only at sinus pressures below the mean arterial blood pressure for the group (Fig. 7). The maximum gain was increased from 0.63 to 0.72 mm Hg/mm Hg CSP and occurred at a carotid sinus pressure of 115 mm Hg, and this increased to 0.78 mm Hg/mm Hg CSP at 101 mm Hg after division \((P > 0.2)\) (Table 2).

In the renal hypertensive rabbits, aortic arch denervation resulted in a significant increase of blood pressure \((P < 0.05)\) at all carotid sinus pressures below 160 mm Hg, the difference being greater at low carotid sinus pressures, and at 60 mm Hg CSP, increases of up to 20 mm Hg were observed (Fig. 7). At their normal blood pressure (134 ± 3.2 mm Hg), aortic nerve division increased blood pres-
Table 2  The Maximum Calculated Gain of the Carotid Sinus Baroreceptor Reflex Control of Blood Pressure, Heart Rate and Hindlimb Vascular Resistance in Normal, Medial Sclerotic, and Renal Hypertensive Rabbits before and after Aortic Nerve Division

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Medial sclerotic</th>
<th>Renal hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of rabbits</td>
<td>12</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>( \Delta \text{BP}/\Delta \text{CSP} ) max. gain (mm Hg/mm Hg CSP)</td>
<td>ANI 0.38 ± 0.03</td>
<td>0.63 ± 0.06 ( P &lt; 0.01 )</td>
<td>0.58 ± 0.5 ( P &lt; 0.05 )</td>
</tr>
<tr>
<td></td>
<td>ANS 0.78 ± 0.06</td>
<td>0.72 ± 0.08 (NS)</td>
<td>0.65 ± 0.06 (NS)</td>
</tr>
<tr>
<td></td>
<td>( P &lt; 0.01 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta \text{HR}/\Delta \text{CSP} ) max. gain (beats/min per mm Hg CSP)</td>
<td>ANI 0.35 ± 0.05</td>
<td>0.23 ± 0.04 ( P &lt; 0.05 )</td>
<td>0.11 ± 0.03 ( P &lt; 0.01 )</td>
</tr>
<tr>
<td></td>
<td>ANS 0.55 ± 0.03</td>
<td>0.30 ± 0.05 ( P &lt; 0.05 )</td>
<td>0.15 ± 0.04 ( P &lt; 0.01 )</td>
</tr>
<tr>
<td></td>
<td>( P &lt; 0.05 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \Delta \text{VR}/\Delta \text{CSP} ) max. gain (VR units/mm Hg CSP)</td>
<td>ANI 0.04 ± 0.01</td>
<td>0.07 ± 0.015 ( P &lt; 0.05 )</td>
<td>0.11 ± 0.02 ( P &lt; 0.01 )</td>
</tr>
<tr>
<td></td>
<td>ANS 0.07 ± 0.01</td>
<td>0.11 ± 0.025 ( P &lt; 0.05 )</td>
<td>0.15 ± 0.03 ( P &lt; 0.01 )</td>
</tr>
<tr>
<td></td>
<td>( P &lt; 0.05 )</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANI = before aortic nerve section; ANS = after aortic nerve section; NS = not significant. Values are means ± SEM. \( P \) values in brackets refer to the difference of the values between ANI and ANS. Other \( P \) values refer to the difference of medial sclerotic and renal hypertensive from normal.

BASAL VASCULAR RESISTANCE mmHg.ml⁻¹.min⁻¹.kg

FIGURE 6  Graph of the relationship between mean femoral artery pressure and “basal” hindlimb vascular resistance in 8 normal (○), 12 medial sclerotic (▲), and 8 renal hypertensive rabbits (●). The line is the regression line (\( r = 0.88, P < 0.01 \)). In the medial sclerotic group there are two observations represented by one symbol at 95/18.8

Heart Rate

Figure 8 shows that after division of the aortic nerves in normal rabbits, the curve relating heart rate to carotid sinus pressure is steeper, the maximum gain being significantly increased \( (P < 0.05) \) (Table 2), and the range of control of heart rate is greater, 45 beats/min, compared to 31 beats/min with the aortic nerves intact. In the medial sclerotic and renal hypertensive groups of animals, aortic arch denervation had little effect on the curves or maximum gain (Fig. 8; Table 2).

Vascular Resistance

In normal and medial sclerotic animals, division of the aortic nerves caused a small increase in vascular resistance at carotid sinus pressures below 120 mm Hg (Fig. 9). The largest effect occurred in the renal hypertensive group, in which the increased vascular resistance was evident over the whole range of carotid sinus pressure (Fig. 9), but was more marked at pressures below 120 mm Hg CSP.

Discussion

These experiments have demonstrated for the first time the changes that occur in the set-point and maximum gain of the carotid sinus baroreceptor control of heart rate, blood pressure and hindlimb vascular resistance in medial sclerotic and renal hypertensive rabbits. Our results corroborate previous findings concerning the control of blood pressure in renal hypertensive rabbits by the subclavian baroreceptor region (Ueda et al., 1966) and have shown the importance of the changes in the relationship of the hindlimb vascular resistance to carotid sinus pressure in mediating blood pressure responses (McCubbin et al., 1956).

Abnormalities of the baroreceptor reflex arc are evident in these experiments and could result from a variety of faults in the system. Most of the effects
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FIGURE 7 Graph of the relationship between carotid sinus pressure and blood pressure before (filled symbols) and after (unfilled symbols) aortic nerve section in 12 normal (N) (○, ●), 20 medial sclerotic (MS) (△, ▲), and 8 renal hypertensive (RH) (□, ■) rabbits. All values are means ± SEM.

Changes in the baroreceptor input are probably secondary to changes of the viscoelastic properties of the arterial wall in which the receptors are situated (Aars, 1969;

FIGURE 8 Graph of the relationship between the heart rate and carotid sinus pressure before (filled symbols) and after (unfilled symbols) aortic nerve section in 12 normal (N) (○, ●), 20 medial sclerotic (MS) (△, ▲), and 8 renal hypertensive (RH) (□, ■) rabbits. All values are means ± SEM.
Angell-James, 1973, 1974a, 1974b), or to changes in the receptors themselves occurring as a result of electrolyte or membrane alterations (Saum et al., 1977). However, the baroreceptor reflex arc also may be modified centrally by changes in the nucleus tractus solitarius (Reis et al., 1977) or other areas in the brain as well as at spinal cord level (Haeusler, 1977). Some of these changes may be explained by alterations of the α-receptors or the concentration of central neurotransmitters. The alterations in the heart rate or vascular resistance response to changes of baroreceptor stimulation in renal hypertensive and medial sclerotic rabbits could result, at least in part, from the manner in which calcium (Aoki et al., 1979) or other electrolytes are having an effect at a cellular level. There is also evidence that vascular sensitivity to angiotension II is modified by prostaglandins in some hypertensive individuals (Yoshimura, 1979). An abnormality in the number of alpha receptors in hypertensive animals also has been postulated as having a bearing on the production and maintenance of the increased vascular resistance. In the present experiments, however, there is no evidence for or against these possibilities, and most of the results can be simply explained on the basis of altered afferent baroreceptor activity in the presence of a raised basal vascular resistance (Folkow, 1971), with an elevated neurogenic tone.

Previous work on baroreceptor control of the cardiovascular system by the carotid sinuses and aortic arch has been concerned partly with the input-output responses of the baroreceptors themselves, and these findings have an important bearing on the interpretation of the present results. As pressure is increased from zero, a threshold pressure is reached at which individual baroreceptor units start discharging. The discharge then increases linearly with pressure, and at the same time new fibers are recruited until a point of inflection is reached when the discharge reaches a plateau or diminishes. At any given pressure the total activity depends on the frequency of discharge in individual fibers and the number of active fibers, whereas the gain or sensitivity depends on the change of the individual baroreceptor fiber discharge produced by a given change of pressure, as well as on the number of additional baroreceptors recruited and their discharge frequency.

In renal hypertension, the carotid sinus baroreceptor fiber activity at any given level of pressure and the gain (discharge frequency per unit change of pressure) are reduced in dog (McCubbin et al., 1956; Sleight et al., 1977) and rabbit (Kezdi, 1962). The curves relating single baroreceptor activity to arterial blood pressure are shifted to the right so that the maximum gain occurs at higher level of pressure (Sleight, 1977).

The aortic arch baroreceptors are affected in a similar way (Kreiger and Marseilian, 1966; Aars, 1968; Angell-James, 1973, 1974a, 1974b; Jones and Thoren, 1977). The reduction in the level of whole nerve activity at any given pressure (McCubbin et al., 1956) is due to a reduction in the frequency of firing in individual fibers and to a loss of baroreceptor units through damage and degeneration (Angell-
James, 1973, 1974a, 1974b). In medial sclerotic animals, the gain of the relationship of impulse frequency and pressure is diminished as in renal hypertensive animals, but in contrast there is no resetting (Angell-James, 1973, 1974b). These changes in the physiological properties of the arterial baroreceptors are due to alterations in the distensibility of the arteries in which the receptors lie (Angell-James, 1973, 1974a, 1974b) and undoubtedly contribute to the diminished baroreflex control of pulse interval, determined by the pressor test, in hypertensive humans (Bristow et al., 1969; Gribbin et al., 1971) and in hypertensive and medial sclerotic rabbits (Angell-James and George, 1976). The degree of modification of the aortic baroreceptor activity in medial sclerotic and renal hypertensive rabbits (Angell-James, 1973, 1974b; Angell-James and George, 1976) and the reduction in baroreflex sensitivity in rabbits (Angell-James and George, 1980) and humans (Bristow et al., 1969; Gribbin et al., 1971) are related to the duration of the disease and to the level of blood pressure.

Heart Rate

The reduction in gain of the carotid sinus control of heart rate without resetting in medial sclerosis can be explained fully on the basis of the known changes in the physiological properties of arterial baroreceptors, as can the reduced gain which is maximal at a higher pressure than normal in renal hypertensive animals. Thus, in renal hypertension, the gain is less than in normal animals at low carotid sinus pressures, but is greater than in normals at pressures above about 160 mm Hg, which is compatible with the known changes that occur in the arterial baroreceptor discharge.

Vascular Resistance

The maximum gain of the curves relating carotid sinus pressure to hindlimb vascular resistance was greater in both medial sclerosis and renal hypertension, and coincided with the mean level of arterial blood pressure in the respective groups. The range of control of vascular resistance from 60 to 200 mm Hg carotid sinus pressure also was greater than normal, particularly in the renal hypertensive group of animals. These findings at first might seem to oppose the concept of reduced baroreceptor activity and sensitivity in these pathological conditions that have been demonstrated previously and for which there is supporting evidence in the present experiments in relation to the control of heart rate. However, other factors must be considered which may be operating under these conditions.

The increased vascular resistance at any carotid sinus pressure may result from either a reflexly increased sympathetic discharge consequent upon the reduced baroreceptor activity and sensitivity, or to the sympathetic nerves acting on vessels with a background of increased basal vascular resistance demonstrated in both groups of pathological animals. Studies in experimental renal hypertension indicate that there is no increase in sympathetic discharge (Kezdi, 1962; Kreiger and Marseillan, 1966) and that the increase in vascular resistance at any blood pressure is determined by a non-autonomic component (West et al., 1975), such as a pathological change in the wall reducing the size of the lumen of the resistance vessels. A mechanism which would explain the increased range of control and maximum gain of the carotid sinus control of hindlimb vascular resistance is suggested by the work of Folkow (Folkow et al., 1958; Folkow and Sivertsson, 1968; Folkow, 1971), that for any degree of smooth muscle shortening the change in flow resistance is larger in a vessel with increased wall:lumen ratio than in a normal one due to a steeper dose-response curve. Thus, for any degree of change of sympathetic excitation, the change in resistance in vessels with an increased wall:lumen ratio would be greater than in normal vessels. This mechanism, operating on the efferent side of the arterial baroreceptor reflex arc, would predict the greater change of vascular resistance over the whole range of carotid sinus pressure used in our experiments in the medial sclerotic and renal hypertensive groups of animals. The fact that the gain of the baroreceptor themselves is reduced, and by inference that of the sympathetic efferent activity as well, does not mitigate against this view; these effects on the afferent side of the reflex arc could be offset by the greater dose-response curve of the vessels occurring secondarily to the higher wall:lumen ratio and vessel reactivity (Folkow et al., 1958).

Blood Pressure

The changes in the cardiac output in response to carotid sinus perfusion pressure are relatively small in normal (Humphreys and Joels, 1977) and renal hypertensive animals (J.E. Angell-James and C. J. Peters, unpublished observations) and the reflex changes in blood pressure therefore are due largely to alterations in total peripheral resistance. This means that the explanation for the reflex changes in blood pressure in the medial sclerotic and renal hypertensive animals compared to the normal group must be similar to that for the changes of hindlimb vascular resistance.

The maximum reflex gain of the curves relating carotid sinus pressure and blood pressure occurred at about the level of the mean blood pressure for each group. However, in the normal group of animals, the maximum gain was situated above the level of the mean blood pressure. Such a finding may be expected from the use of non-pulsatile perfusion of the carotid sinus (Angell-James and Daly, 1970, 1971).

In hypertensive rabbits and rats the afferent baroreceptor responses to pulsatile pressures are similar to those of normotensive animals (Angell-James, unpublished observations, Brown et al., 1978; Nosaka et al., 1972; Sleight et al., 1977) al-
though they are reset to a higher pressure and the number of impulses per cycle is reduced (Sleight, 1977). In our renal hypertensive rabbits the gain fell rapidly below 120 mm Hg when the vascular resistance was high; that is, at a pressure in normal animals when the gain is at a maximum, and this is compatible with the view that in renal hypertensive animals the baroreceptor impulse frequency-pressure curves are shifted markedly to the right (Aars, 1968; Angell-James, 1973; Brown et al., 1978; Kezdi, 1962; Kreiger et al., 1966; McCubbin et al., 1966; Sleight et al., 1977). Thus, hypertensive animals are less able to resist hypotensive states than normal animals but better able to resist hypertension.

Previous studies of the baroreceptor control of blood pressure in hypertensive animals have indicated that this control is either normal (McCubbin et al., 1956; Alexander and DeCuir, 1966; Ueda et al., 1966) or that blood pressure responses are exaggerated (Bouckaert et al., 1937). These views, however, neglect the factors that are fundamental to the reflex control of heart rate and vascular resistance. It thus is suggested that, with respect to blood pressure control, the results from the opposing influences of reduced baroreceptor sensitivity and increased vascular reactivity must be taken into account.

**Modification by Aortic Baroreceptors**

The difference in the shapes of the curves relating carotid sinus pressure and blood pressure before and after aortic nerve division in the three groups of rabbits must be due to the relative activity of the aortic baroreceptors in each group. Thus, in the normal rabbit, they oppose both carotid sinus-induced hypotension and hypertension, which is in accord with the previous findings that rabbit aortic arch baroreceptors are active at normal blood pressures (Aars, 1968). By contrast, the aortic arch baroreceptors were unable to modify carotid sinus-induced reflex hypotension in either the medial sclerotic or renal hypertensive groups, but had a slight effect on carotid sinus-induced hypertension; this latter effect may be partly the result of enhancement by increased vascular reactivity at the higher vascular resistance (Folkow and Sivertsson, 1968). This ineffectiveness of the aortic arch baroreceptors is predictable on the basis of previous investigations demonstrating their reduced gain and resetting in the two conditions (Angell-James, 1973, 1974b). It should be noted, however, that in the renal hypertensive rabbits the further resetting of blood pressure after aortic nerve section would indicate that these receptors were having an anti-hypertensive effect. This observation may be relevant to the finding in chronic renal hypertension that, although the activity in myelinated fibers from the aortic arch baroreceptors is reduced, in non-myelinated fibers it may be increased (Jones and Thoren, 1977). It follows that the aortic arch baroreceptors in renal hypertension, being reset to function maximally at higher pressures than normal (Aars, 1968; Angell-James, 1973), would exert their most powerful anti-hypertensive effect at blood pressures between 120 and 160 mm Hg, that is, when the carotid sinus pressures are low (Fig. 7). At high carotid sinus pressures (low aortic pressures) they would be relatively inactive; this is in contrast to the normal rabbits in which the aortic baroreceptors would be functionally most active at these pressures and thus able to counteract the carotid sinus-induced hypotension (Fig. 7).

In the medial sclerotic group of animals, the inability of the aortic arch baroreceptors to modify the carotid sinus responses is due to the aortic wall being severely diseased with a consequent reduction of baroreceptor activity (Angell-James, 1974b). Medial sclerosis starts in the ascending aorta and progresses toward the periphery so that the baroreceptors in the aorta would be expected to be affected more severely than those in the carotid sinuses. By comparison, the aortic baroreceptors were unable to modify the heart rate responses to changes of carotid sinus pressure in medial sclerotic and renal hypertensive animals when compared with normals, a finding which is in keeping with the known reduced aortic baroreceptor sensitivity in these conditions (Angell-James, 1973, 1974b).

**Clinical Implications**

From data obtained in these experiments illustrating the changes of baroreceptor reflex control of the circulation in hypertensive rabbits, it becomes apparent that if a similar situation occurs in hypertensive patients they would have poor control of their blood pressure when it falls suddenly to low pressures as a result of hemorrhage or shock, or following intensive anti-hypertensive treatment. The result could be a profound fall in cerebral blood flow giving rise to cerebral hypoxia or thrombosis. Likewise, in normotensive people who suddenly develop hypertension following the ingestion of tyramine-containing foodstuffs when they are taking monoamine oxidases, one would anticipate that they would be unable to counteract this hypertension adequately since the pressure would be at a level where the baroreceptors have minimum gain. Treated hypertensive patients in whom the baroreceptors have reset to a lower pressure might be in a similar position when they become hypertensive on withdrawal of treatment, as in the case of clonidine.

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