Vascular Amplifier Properties in Renovascular Hypertension in Conscious Rabbits

Hindquarter Responses to Constrictor and Dilator Stimuli

CHRISTINE E. WRIGHT, JAMES A. ANGUS, AND PAUL I. KORNER

SUMMARY The local responses of the resistance vessels of the hindquarters of conscious, renal hypertensive (cellophane wrap) and sham-operated normotensive rabbits were studied during infusions of constrictor (norepinephrine, methoxamine, angiotensin II) and dilator (acetylcholine, adenosine, serotonin) drugs. The rabbits had implanted Doppler ultrasonic flow probes on the lower aorta and an indwelling catheter for intra-arterial infusion of drugs. Autonomic blockade with mecamylamine and propranolol was used to determine local vascular effects of each drug uncomplicated by reflex changes. Logistic dose-vascular response curves were characterized by (1) their range from resting to maximum response, (2) their 50% effective dose (i.e., sensitivity or dose at middle of the response range), and (3) the average slope about the 50% effective dose. At maximum dilatation the vascular resistance was about 70% greater in hypertensive rabbits than in normotensive rabbits. There were no significant differences in 50% effective dose values between curves for hypertensive and normotensive rabbits for constrictor or dilator drugs. However, with all drugs the hypertensive rabbits showed about twice the change in vascular resistance per unit dose compared with the normotensive rabbits. These results suggest that hypertrophy of the muscles of the precapillary vessels makes them a nonspecific amplifier of vascular resistance changes evoked by constrictor and dilator stimuli. They do not support previous claims of specific changes in “sensitivity” or claims that local amplifier action is unimportant in hypertension. (Hypertension 9: 122-131, 1987)

KEY WORDS amplifier properties • constrictors • dilators • hypertension • vascular reactivity

The amplifier properties of the hypertrophied vascular and cardiac musculature in primary and many types of secondary hypertension have been considered to play a role in the hemodynamic patterns of hypertension and most circulatory responses.1,2 Folkow et al.3 pointed out that the associated increase in the ratio of the wall thickness to lumen radius was important in making the small arteries and arterioles hemodynamic amplifiers of stimuli affecting vascular resistance. As a result, a given dose of constrictor agent or a given percentage shortening of the muscle would produce more pronounced vascular narrowing in hypertension than in normal vessels. This response has now been demonstrated in the isolated vessels of the limb and kidney in spontaneously hypertensive rats (SHR), in rats with renal hypertension, and in the cutaneous circulation of patients with primary hypertension.1,2 We have confirmed these amplifier properties in conscious rabbits with established renovascular (cellophane wrap) hypertension in which reflex influences on the circulation were abolished by autonomic blockade.4 Moreover, we found similar enhancement of responsiveness to norepinephrine, angiotensin II, and vasopressin, which is in accord with nonspecific amplifier properties, as would be expected from the structural changes in hypertension.5,6

Recently, Hamilton and Reid7 observed a selective change in blood pressure responsiveness to α1-adrenergic receptor agonists in rabbits with cellophane wrap hypertension. In contrast to our findings they observed a leftward shift of their dose–mean arterial pressure response curves in the hypertensive rabbits with no change in slope, which suggested an increase in responsiveness. Earlier Fink and Brody8 had reported that changes in renal vascular resistance to norepinephrine were less in the intact renal circulation of SHR compared with normotensive rats. This group has re-
ported that in conscious adult rats treated with hexamethonium the renal and hindquarter resistance changes to norepinephrine were depressed (lower slope) in SHR compared with control rats. Both sets of findings have challenged the importance of the vascular amplifier in the in situ circulation in hypertension and are in direct conflict with our earlier findings.

One major difference in methodology was that in the experiments of Hamilton and Reid and in most of those of Brody and colleagues, autonomic function remained intact, so that the circulatory responses depended on the sum of local and reflex changes (see Discussion). By contrast, Folkow et al. studied the local properties of isolated, perfused vascular beds, and this was also largely the case in our experiments in conscious animals in which autonomic reflexes were eliminated. Another difference was that we studied the effects of drugs on vascular resistance in our earlier studies, whereas Hamilton and Reid measured only blood pressure responses, which depend not only on resistance changes but also on cardiac factors.

The purpose of the present study was to reexamine the local properties of the resistance vessels of the hindquarter in hypertensive rabbits. As before, we used conscious rabbits subjected to "total" autonomic blockade to prevent reflex changes in the intact animal that are inevitable during the administration of agonist drugs. We have extended our previous study by obtaining sigmoid dose–vascular response curves to a range of both constrictor and dilator agents to resolve the question of the specificity or nonspecificity of the vascular responsiveness. To obtain maximum constrictor and dilator responses, we infused the drugs intra-arterially into the lower abdominal aorta, in contrast to most previous studies in intact animals, which used intravenous administration. The term vascular reactivity has been defined in a variety of ways (see References 11–13), which has led to some confusion. In the present study, we have characterized the agonist dose–vascular response curves in the standard pharmacological manner (see Methods).

Materials and Methods

The study was approved by an animal ethics committee in accordance with the guidelines of the National Health and Medical Research Council of Australia.

Animals and Operations

We used male and female rabbits developed from an English multicolored strain. The average weight of the rabbits was 2.3 kg (range, 2.0–2.8 kg). A preliminary operation was performed with the rabbits under open circuit halothane anesthesia after induction with propanidid (Eptonol), 30 mg/kg, i.v. A flow transducer (inside diameter, 4 mm) for measuring hindquarter flow by the pulsed Doppler technique was placed around the lower abdominal aorta just proximal to the iliac bifurcation. A fine polyvinylchloride catheter was implanted in the aorta approximately 1 cm above the flow probe and was filled with heparin, 1000 U/ml, and the other end was sealed. The catheter and the transducer lead wires were led subcutaneously to the back of the neck. Both kidneys were exposed and wrapped in cellophane, as described previously. The ends of the cellophane were gathered at the hilum and secured loosely with a silk tie. In control experiments, we performed a sham operation in which the rabbit's kidneys were exposed but not disturbed. The rabbits received rolitetracycline, 40 mg/kg i.m. (Reverin), at the end of the operation.

On the day of the experiment, the lead wires from the flow probe and the end of the aortic catheter were retrieved under local anesthesia (0.5% lignocaine hydrochloride, Xylocaine). The flow transducer was connected to a pulsed Doppler flowmeter (Model 545C-3; Bioengineering, University of Iowa, Iowa City, IA), and the aortic catheter was prepared for infusions of the vasodilator and vasoconstrictor agents. The central ear artery and vein were cannulated with the rabbits under local anesthesia. The ear artery catheter was connected to a Statham P23Db pressure transducer (Gould, Saddle Brook, NJ, USA), and the mean and phasic arterial pressure (MAP) were recorded on a Grass polygraph (Model 7; Quincy, MA, USA). Other variables recorded were lower aortic blood flow and heart period (pulse interval; see Figure 1). Hindquarter vascular resistance (MAP/flow) or conductance (flow/MAP) was computed continuously by an analog computer.

Protocol

The catheter was flushed once a week with 0.9% NaCl, then filled with heparin, 1000 units/ml. All rabbits were studied 5 weeks postoperatively. For inclusion in the study, the renal-wrapped rabbits needed to have a MAP of 120 mm Hg or more. Eight renal-wrapped rabbits with MAP between 90 and 100 mm Hg 5 weeks postoperation were excluded from the study. Four hypertensive rabbits died 4 to 5 weeks after operation of either cerebral hemorrhage or renal failure.

After the minor procedures on the day of the experiment, the rabbit sat quietly in a wooden box for approximately 30 minutes. Its autonomic effectors were then blocked with the ganglion blocker mecamylamine, 10 mg/kg i.v., given over 10 minutes in 10 ml 5% dextran (Rheomacrodex), which completely abolished the nasopharyngeal reflex elicited by cigarette smoke for over 4 hours (C.E. Wright, J.A. Angus, unpublished observations, 1985). In addition it abolished the constrictor response to hemorrhage. Propranolol, 0.5 mg/kg i.v. bolus, also was administered to block cardiac and vascular dilator effects of infused norepinephrine. The animals received another dose of mecamylamine (4 mg/kg i.v. bolus) after 4 hours.

Infusion of Agonist Drugs

To allow construction of dose-response curves to a particular agonist, the autonomically blocked rabbit received intra-aortic infusions of increasing doses of agonist in volumes of 0.08 to 3.24 ml/min; 0.9% NaCl given over this range of infusion rates had no effect on
regional hemodynamics. Each dose was infused until a steady state of MAP and hindquarter flow had been reached (i.e., about 3 min; Figure 1). After one dose-response curve had been completed, a 30-minute rest period was allowed before the effects of the next agonist were tested. Norepinephrine (0.03-6.0 μg/kg/min) was infused first, followed by, in random order, methoxamine (0.3-60 μg/kg/min), angiotensin II (0.03-3.0 μg/kg/min), acetylcholine (0.3-60 μg/kg/min), and adenosine (3-600 μg/kg/min). After these five drugs had been tested, the rabbit received ketanserin (0.5 mg/kg i.v. bolus), which antagonized the effects of serotonin on 5-hydroxytryptamine receptors. Ten minutes later, a dose-response curve was constructed to an intra-aortic infusion of serotonin (3-120 μg/kg/min).

Drugs

Drugs used were freshly prepared each day and included acetylcholine bromide (Sigma Chemical, St. Louis, MO, USA), adenosine (Sigma), angiotensin II amide (Hypertensin; CIBA-Geigy, Basel, Switzerland), 5-hydroxytryptamine creatinine sulfate (Sigma), ketanserin tartrate (R49945; Janssen, Beerse, Belgium), mecamylamine hydrochloride (Merk Sharp & Dohme, Rahway, NJ, USA), methoxamine hydrochloride (Wellcome Foundation, London, UK), norepinephrine acid tartrate (Levophed; Winthrop, Melbourne, Australia) and propranolol hydrochloride (ICI, Melbourne, Australia). Drug doses were considered as their salts and diluted in 0.9% NaCl. Mecamylamine was administered in 10 ml of Rheomacrodex (ICI, Melbourne, Australia). Drug doses were considered as their salts and diluted in 0.9% NaCl. Mecamylamine was administered in 10 ml of Rheomacrodex (10% dextran 40 in dextrose, Pharmacia, Melbourne, Australia).

Analysis of Dose–Vascular Response Curves and Statistical Methods

We constructed sigmoid logistic dose–vascular response curves as described previously, using absolute values. The responses were expressed as a percentage of the maximum effect of each agonist, and from each fitted curve values for the doses at effective dose 10% (ED10), 30% (ED30), 50% (ED50), 70% (ED70), and 90% (ED90) were obtained. The sigmoid dose–absolute response curves were characterized in the usual way using (1) range from resting to plateau of the maximum response, (2) ED50, or the dose corresponding to half-maximum response, and (3) the average slope and -1 standard deviations about the ED50. The average slope was calculated by a sigmoid logistic curve fitted to the absolute responses for each agonist. For each constrictor and dilator drug, we derived both dose-vascular conductance curves and dose-vascular resistance curves. For the statistical comparisons of hypertensive and sham-operated rabbits, we used (1) dose–vascular resistance curves for the dilator drugs and (2) dose–vascular conductance curves for the constrictor drugs (see Results). The advantage is that with increasing doses of dilator drugs the vascular resistance falls to a clear minimum plateau value while conductance tends to keep increasing with a less well-defined plateau and increased heteroscedasticity of variances. The opposite occurs with constric-tor drugs: with increasing doses, the limit of response is zero conductance with high drug doses and a tendency for vascular resistance to approach infinity and its variance to increase. The use of resistance for dilator drugs and conductance for constrictor drugs allows more rigorous comparisons of the dose-response curves of the hypertensive and normotensive rabbits. Clearly, since conductance and resistance are the reciprocals of one another, they measure the same vascular properties (see Discussion).

Average SEM within animals for hindquarter vascular resistance or conductance was calculated from two-way analysis of variance (ANOVA) as (error mean square/number of animals)^0.5 after subtracting the sums of squares between animals and between doses from the total sums of squares for each agonist. This error bar (± 1 average SEM) is located on the average dose-response line for each group (see Figures 3–5). Parameters of dose–vascular response curves to vasodilator or vasoconstrictor agents — slope, range, ED50, and plateau values — were compared between groups by unpaired t test (see Tables 2 and 3). Circulatory variables at rest were compared between groups by unpaired t test (see Table 1). Within each group, circulatory variables before and after autonomic blockade were compared by paired t test (see Table 1). Analysis of covariance was used to test slopes and intercepts of multiple regression lines from the Doppler flow transducer calibrations.

Doppler Transducer Fabrication and Calibration

The Doppler ultrasonic flow transducers were constructed as described previously. The cuffs were fabricated on a stainless steel rod (diameter, 4 mm) covered with Dacron Cooley Graft (Dupont, Wilmington, DE, USA) vascular prosthesis. These Dacron-sheathed flow transducers became firmly attached by granulation tissue to the adventitial surface of the aorta about 4 to 5 weeks after implantation. The Dacron sheath was important for measuring volume flow by producing firm attachment between transducer cuff and vessel and preventing falls in vascular diameter during falls in blood pressure.

To test the linearity of the Doppler shift with volume flow, we calibrated six transducers in situ in normal rabbits over the pressure range 50 to 150 mm Hg; we have shown previously that the calibration is similar in hypertensive animals. The rabbits were heparinized (300 U/kg i.v.) and then killed with pentobarbitone. The lower abdominal aorta proximal to the implanted transducer and the two iliac vessels were cannulated with polyethylene tubing, and the small branches were tied off or clamped. Heparinized blood was pumped by a roller pump from a reservoir through the aorta and returned through a collecting cylinder. The outflow resistance from the two iliac cannulas was varied by a screw clamp to keep the mean pressure measured just distal to the flow transducer at 50, 100, or 150 mm Hg. Volume flow was varied from 25 to 150 ml/min by changing the speed of the roller pump.

Because there were no significant differences be-
between the slope or intercepts of the regression lines relating Doppler shift and blood flow at the three pressures, we have pooled the data in Figure 2B. The slopes of the relationships between Doppler shift and flow were similar in all six rabbits, but there were small, statistically significant differences in intercept values ($p < 0.05$). There was no evidence of curvature, and the overall regression line for the six transducers passed very close to zero intercept (Figure 2A). For a blood flow of 100 ml/min, the average Doppler shift was 6.9 kHz. As the relationship between kilohertz shift and volume flow was linear, every flow transducer was calibrated precisely against volume flow. Therefore, flow has been measured in units of kilohertz of Doppler shift.

Results

Resting Circulatory Variables Before and During Autonomic Blockade

Five weeks postoperatively, the hypertensive rabbits had MAPs that were 57% above the average value of the sham-operated rabbits and a hindquarter vascular resistance that was 116% higher ($p < 0.01$; Table 1). The hindquarter blood flow tended to be lower in the hypertensive rabbits than in the sham-operated animals, but the difference was not statistically significant.

Autonomic blockade (see Methods) resulted in falls in MAP and in hindquarter vascular resistance that were about two to three times greater in the hypertensive than in the normotensive rabbits (i.e., MAP fell by 21 and 12 mm Hg, respectively, in hypertensive and normotensive rabbits; corresponding figures for hindquarter vascular resistance were 16.7 and 5.3 mm Hg/kHz). After blockade, MAP and hindquarter vascular resistance of the hypertensive rabbits were still well above corresponding values of sham-operated rabbits, but heart rate and hindquarter blood flow between groups were not significantly different ($p < 0.05$; see Table 1).

Infusion of Dilator Drugs

The dose–hindquarter vascular resistance response curves (see Methods for reason for using resistance) during infusion of acetylcholine, adenosine, and serotonin differed significantly between sham-operated and hypertensive rabbits (Figure 3, top panels; Table 2). Within each group the responses to each dilator agent were similar: when the dose-response curves were expressed in absolute units of vascular resistance, the slope, range, and resting vascular resistance of the curves in the hypertensive rabbits were approximately double the corresponding values in sham-operated rabbits (see Table 2). When the dose–hindquarter vascular resistance relationship was expressed as the percentage of each animal’s maximum response, there was no significant difference in $ED_{50}$ between sham-operated and hypertensive rabbits (see Figure 3, bottom panels). Expressing the data in this way rather than in absolute units removed the previous differences in range and slope.

With all agents, the maximum degree of vasodilation elicited falls in MAP, and large rises in hindquarter blood flow were similar for all three drugs. In sham-operated rabbits, the average resting blood pressure for all three drugs was 63.2 mm Hg and fell to 48.9 mm Hg at maximum dilatation; corresponding values for hindquarter blood flow were 4.6 and 8.3 kHz. In hypertensive rabbits, MAP was 103.3 mm Hg at rest and 77.2 mm Hg at maximum dilatation; blood flow changed correspondingly from 4.1 kHz to 7.9 kHz. The fall in MAP only occurred at the higher dose range of each drug. At up to 50% of the maximum increase in hindquarter blood flow from resting, there was no significant change in systemic MAP.
FIGURE 2. A. Linear regression lines from six transducers relating blood flow to Doppler shift in different rabbits. Each line is the average from the points measured at perfusion pressures of 50, 100, and 150 mm Hg, which were not significantly different. The dotted line indicates the average line for all six transducers. B. Values obtained during calibration of one transducer at perfusion pressures of 50 (●), 100 (●), and 150 (○) mm Hg. The line shown is the average regression line.

![Graph showing linear regression lines for blood flow versus Doppler shift](image)

TABLE 1. Circulatory Effects of Autonomic Blockade on Sham-operated and Hypertensive Rabbits

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sham-operated (n = 7)</th>
<th>Hypertensive (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Block</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>79.4 ± 2.0</td>
<td>67.4 ± 2.2*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>171.3 ± 8.7</td>
<td>271.7 ± 12.0*</td>
</tr>
<tr>
<td>Hindquarter Blood flow (kHz)</td>
<td>4.25 ± 0.38</td>
<td>5.18 ± 0.56*</td>
</tr>
<tr>
<td>Vascular resistance (mm Hg/kHz)</td>
<td>19.5 ± 1.7</td>
<td>14.2 ± 2.0*</td>
</tr>
</tbody>
</table>

Values are means ± 1 SEM. Values during block were taken 20 minutes after administration of mecamylamine and propranolol. SED = standard error of the difference within animals.

*p < 0.05, compared with control value (paired t test).

Infusion of Constrictor Drugs

We derived dose–absolute hindquarter vascular conductance response curves for norepinephrine, methoxamine, and angiotensin II, as explained in Methods. Again, the dose–absolute conductance curves of all the drugs were similar (Figure 4, top panels; Table 3). Resting hindquarter vascular conductance, slope, and range of the dose-response curves in the hypertensive rabbits were about half the values observed in the normotensive animals (note: conductance = 1/resistance for comparison with dilator drugs). When the results were expressed as a percentage of the maximum constrictor response (Figure 4, bottom panels), there was no significant difference between ED₅₀ values or any of the curve parameters.

Most previous studies have expressed vascular ef-

![Graph showing average values of relationship between drug dose and hindquarter resistance](image)
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### TABLE 2. Parameters of Dose-Induced Vascular Resistance Curves During Administration of Dilator Drugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham-operated (n = 7)</th>
<th>Hypertensive (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting hindquarter vascular resistance (mm Hg/kHz)</td>
<td>14.6 ± 1.3</td>
<td>30.9 ± 4.8*</td>
</tr>
<tr>
<td>Range (Δ resistance units)†</td>
<td>8.2 ± 1.0</td>
<td>20.9 ± 4.0*</td>
</tr>
<tr>
<td>Average slope</td>
<td>−6.10 ± 1.29</td>
<td>−18.10 ± 5.63*</td>
</tr>
<tr>
<td>ED₅₀ (log₁₀ [ng/kg/min])</td>
<td>3.22 ± 0.12</td>
<td>3.13 ± 0.13</td>
</tr>
<tr>
<td>Adenosine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting hindquarter vascular resistance (mm Hg/kHz)</td>
<td>16.6 ± 1.4</td>
<td>28.6 ± 4.5*</td>
</tr>
<tr>
<td>Range (Δ resistance units)†</td>
<td>10.7 ± 1.1</td>
<td>18.7 ± 3.3*</td>
</tr>
<tr>
<td>Average slope</td>
<td>−7.31 ± 0.35</td>
<td>−11.72 ± 0.91*</td>
</tr>
<tr>
<td>ED₅₀ (log₁₀ [ng/kg/min])</td>
<td>4.51 ± 0.07</td>
<td>4.58 ± 0.10</td>
</tr>
<tr>
<td>Serotonin (after ketanserin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting hindquarter vascular resistance (mm Hg/kHz)</td>
<td>16.9 ± 4.2</td>
<td>29.9 ± 6.8*</td>
</tr>
<tr>
<td>Range (Δ resistance units)†</td>
<td>7.0 ± 1.3</td>
<td>12.2 ± 2.3</td>
</tr>
<tr>
<td>Average slope</td>
<td>−5.22 ± 1.24</td>
<td>−10.01 ± 3.34*</td>
</tr>
<tr>
<td>ED₅₀ (log₁₀ [ng/kg/min])</td>
<td>4.06 ± 0.04</td>
<td>3.92 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± 1 SEM.  
*p < 0.05, between groups (unpaired t test).  
†From resting value to maximum response.

Effects in resistance units, and this has been done in Figure 5. It is evident that neither the upper plateau nor the ED₅₀ value can be rigorously determined. However, the slope of the quasi-linear part of the curve is, as would be expected from the conductance data, about twice as large in the hypertensive rabbits as in the normotensive animals.

Again, MAP changes were relatively small during the lower doses of i.a. infusion of the constrictor agents, when (at 50% maximum decrease in hindquarter flow) pressure increased by an average of 12.9 mm Hg in the hypertensive and by 14.2 mm Hg in the sham-operated rabbits. At maximum constriction, with conductance close to zero, the MAP had increased from an average resting value of 66.4 mm Hg to 115.6 mm Hg for the three drugs in the sham-operated rabbits, and from 107.8 mm Hg to 150.5 mm Hg in the hypertensive rabbits. Hindquarter blood flow fell correspondingly from an average resting value of 4.65 kHz to 0.43 kHz during maximum constriction with the three drugs in the sham-operated rabbits, and from 4.0 kHz to 0.29 kHz in the hypertensive rabbits (see Figure 1).

### Effects of Norepinephrine Before and After Autonomic Blockade

To illustrate the importance of areflexic preparations, we have compared the pressor and heart period responses to different i.v. boluses of norepinephrine in a normotensive rabbit before and after mecamylamine administration. Before ganglion block, the pressor responses to norepinephrine, 0.4 and 1.6 μg/kg, were associated with marked bradycardia (Figure 6). After mecamylamine, only a quarter of the dose was required to produce the same rise in blood pressure (i.e.,...
### Table 3. Parameters of Dose—Hindquarter Vascular Conductance Curves During Administration of Constrictor Drugs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham-operated (n = 7)</th>
<th>Hypertensive (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting hindquarter vascular conductance ([kHz/mm Hg] × 100)</td>
<td>7.54 ± 0.61</td>
<td>4.12 ± 0.73*</td>
</tr>
<tr>
<td>Range (Δ conductance units)†</td>
<td>7.11 ± 0.59</td>
<td>3.93 ± 0.70*</td>
</tr>
<tr>
<td>Average slope</td>
<td>−5.65 ± 0.56</td>
<td>−2.91 ± 0.81*</td>
</tr>
<tr>
<td>ED50 (log10 [ng/kg/min])</td>
<td>2.21 ± 0.16</td>
<td>2.35 ± 0.22</td>
</tr>
<tr>
<td>Methoxamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting hindquarter vascular conductance ([kHz/mm Hg] × 100)</td>
<td>7.05 ± 0.80</td>
<td>3.70 ± 0.54*</td>
</tr>
<tr>
<td>Range (Δ conductance units)†</td>
<td>6.62 ± 0.72</td>
<td>3.56 ± 0.55*</td>
</tr>
<tr>
<td>Average slope</td>
<td>−5.94 ± 1.29</td>
<td>−2.98 ± 0.59*</td>
</tr>
<tr>
<td>ED50 (log10 [ng/kg/min])</td>
<td>3.89 ± 0.05</td>
<td>3.85 ± 0.14</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting hindquarter vascular conductance ([kHz/mm Hg] × 100)</td>
<td>6.63 ± 0.50</td>
<td>3.35 ± 0.57*</td>
</tr>
<tr>
<td>Range (Δ conductance units)†</td>
<td>6.35 ± 0.51</td>
<td>3.13 ± 0.50*</td>
</tr>
<tr>
<td>Average slope</td>
<td>−7.63 ± 1.20</td>
<td>−2.85 ± 0.47*</td>
</tr>
<tr>
<td>ED50 (log10 [ng/kg/min])</td>
<td>1.96 ± 0.06</td>
<td>1.81 ± 0.08</td>
</tr>
</tbody>
</table>

Values are means ± 1 SEM.  
*p < 0.05, between groups (unpaired t test).  
†From resting value to maximum response.

The pressor sensitivity increased about four times) and there was no reflex bradycardia (see Figure 6).

### Rabbit Body Weight

Rabbits in both the sham-operated and renal-wrapped groups gained weight at approximately the same rate during the postoperative period. On the experimental day (5 weeks postoperatively), there was no significant difference between weights in the sham-operated and hypertensive groups (2.69 ± 0.07 and 2.54 ± 0.08 kg, respectively).

### Discussion

In defining regional vascular responses in the conscious animal, it is not possible to perfuse a given region at constant blood flow, as has been done in comparing vascular responses of isolated hindquarter of rats with genetic hypertension and normotensive controls (e.g., see Folkow et al.). But we have shown that by appropriate choice of variable (i.e., vascular resistance for dilator responses and conductance for constrictor responses) it was possible to derive logistic dose—vascular response curves, where all parameters including the range from resting value to maximum response, the slope, and ED50 could be defined by standard pharmacological dose-response analysis.

This allowed rigorous comparison of the different parameters in the hypertensive and normotensive rabbits. Another important feature was the use of local intrarterial infusions of drugs in the conscious rabbit, which allowed us to obtain maximum dilator and constrictor responses. By contrast, in our previous work in autonomically blocked rabbits, we used only constrictor drugs given by the intravenous route in doses that did not produce maximum constriction.

Our findings with dilator drugs were that at maximum dilatation the vascular resistance was significantly higher in the hypertensive than in the normotensive circulation at similar flows. This finding is in accord with the hypothesis of Folkow and colleagues of medial encroachment on the vessel lumen. We found that range and slope of the dose-response curves were about twice as great in hypertensive as in normotensive controls but there was no change in ED50. Moreover, there were no differences in the effects of any of the drugs on these parameters. Similarly with all three constrictor drugs, conductance (1/resistance), range, and slope in the hypertensive rabbits were about half the values in the normotensive controls and ED50 again was unchanged. The similarity of the relative vascular effects produced by the different agonist drugs (which act through different types of membrane receptors) in the hypertensive and normotensive rabbits is in accord with the nonspecific vascular amplifier properties of the hypertrophied hypertensive vessels. The absence of any difference in ED50 suggests that the threshold sensitivity of the hypertrophied muscle was not changed.

In Figure 7 we have reconstructed the data from our areflexic rabbits to show the changes from resting values in hindquarter vascular resistance during the infusion of both dilator and constrictor drugs. For the reasons considered in Methods, the maximum constrictor effects on vascular resistance are poorly defined, but the graph shows unequivocally that the slope of the dose-response curve is twice as great in hypertension...
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**Figure 6.** Effects of two doses of norepinephrine in a normotensive rabbit on mean (BP) and phasic blood pressure (BP) and heart period (HP) before (left of arrow) and after (right of arrow) administration of mecamylamine, 10 mg/kg.

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**Figure 7.** Top panel. Schematic dose-vascular resistance response curves based on present analysis, showing rabbit hindquarter vascular resistance changes from resting value (circles) during administration of constrictor drugs in hypertensive and normotensive rabbits. Note difference between groups in resistance at maximum dilatation and in slopes. Since constant flow perfusion cannot be used in conscious animals, constrictor maximum is ambiguous (see text). Bottom panel. Schematic results, based on work of Folkow et al., from constant flow perfusion of isolated hindquarter of SHR and Wistar-Kyoto rats. In this case the hindquarter vascular bed starts from maximum dilatation and reaches an easily defined maximum perfusion pressure during norepinephrine infusion because the experiment is conducted at constant flow. It is important to emphasize here that, in the isolated hindquarter preparation, only one dose-response curve to a constrictor agent can be constructed per rat because of the tissue damage caused by this procedure. In the autoperfused, areflexic, conscious rabbit, multiple stimulus-response curves can be readily determined in the same rabbit in 1 day without causing deterioration, as judged by the absence of significant changes in the resting variables.

Our protocol differs in a number of respects from that of Hamilton and Reid, who used rabbits with intact reflexes and studied only changes in blood pressure. Our use of autonomically blocked rabbits prevented changes in vascular tone through various baroreceptor reflexes that are brought into play in the intact animal when the blood pressure changes during drug infusions. Even though we gave the latter intra-arterially, it was not possible to prevent some systemic effects, especially at the higher dose range of the different drugs. Interactions on vascular tone between the local and reflexly evoked effects of the drugs would be even more pronounced if the latter were given by the intravenous route, where the systemic effects would be even greater. The extent of this effect is apparent in Figure 6, showing the greater sensitivity of the preparation, as evident from a fourfold shift in the norepinephrine dose–MAP response curve after blocking of the autonomic effectors. Without the use of this type of areflexic preparation, it is not possible to assess local vascular effects (see above). Moreover, since the properties of the arterial baroreceptors themselves are

Through a large range of vascular tone and that there is no difference in threshold of resistance increases from maximum dilatation. The graph also displays reconstructed data for hindquarter perfusion pressure curves from SHR and Wistar-Kyoto rats. In this case the hindquarter vascular bed starts from maximum dilatation and reaches an easily defined maximum perfusion pressure during norepinephrine infusion because the experiment is conducted at constant flow. It is important to emphasize here that, in the isolated hindquarter preparation, only one dose-response curve to a constrictor agent can be constructed per rat because of the tissue damage caused by this procedure. In the autoperfused, areflexic, conscious rabbit, multiple stimulus-response curves can be readily determined in the same rabbit in 1 day without causing deterioration, as judged by the absence of significant changes in the resting variables.

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impaired in hypertension,22 without the use of autonomic block any differences in the dose-response curve parameters between the hypertensive and normotensive rabbits will be confounded by the opposing effects of the local vascular properties (which are enhanced in hypertension) and the arterial baroreceptor properties (which are impaired). We also suggest that change in MAP is not necessarily an index of vascular responsiveness, since arterial pressure will depend on both vascular and cardiac factors, the latter complicating interpretation, especially during i.v. administration of drugs.

Our protocol blocked the autonomic effectors, but there could be drug-induced changes in circulating hormone concentrations. Hiwatari et al.23 recently showed that immediately after pentolinium-induced autonomic block there was transient release of angiotensin II and vasopressin, which helped to maintain blood pressure. However, we believe that circulating hormones played only a small role in accounting for the response differences between hypertensive and normal rabbits, since (1) the elevations of hormone concentrations demonstrated by Hiwatari et al.23 were only transient and would be small 20 minutes after giving blocking drugs when we obtained our first dose-response curve; (2) the differences in dose–vascular response curves between hypertensive and normal rabbits were similar with all drugs, some of which would produce differential changes in hormone concentrations; (3) there was no time-dependence on resting blood pressure and vascular resistance over the entire time course of the experiment.

One difference between our study and that of Hamilton and Reid7 was that they measured changes 6 to 10 days after wrapping, while we measured them on only one occasion 5 weeks after wrapping. Since the changes described by Hamilton and Reid7 were maintained indefinitely, we should have observed them at the time of our experiment. Another difference was that we wrapped both kidneys in cellophane, while they wrapped one and removed the other. We have previously found that with these two models there is little, if any, difference in the magnitude of the hypertension.24

Our findings suggest that the local properties of the resistance vessels in the intact, conscious rabbit resemble closely the properties previously demonstrated in isolated vascular beds by Folkow et al.3 In the intact animal, use of preparations in which circulatory reflexes are eliminated is critical for demonstrating local vascular effects. Claims by other authors that the vascular amplifier properties are unimportant7-9 probably indicate a failure to take this factor into account.

Reduction of the cross-sectional area of the vascular bed caused by loss of tissue is another mechanism that could account for the differences in slopes and response ranges between the dose-response curves of the hypertensive and normotensive rabbits. We believe that this mechanism is less likely to account for the observed changes than the structural changes associated with hypertrophy in a bed with normal numbers of precapillary vessels, because of (1) strong morphometric evidence of the changes in wall/lumen ratio in chronic hypertension23 and (2) the good conditions of the hypertensive rabbits, which had no signs of wasting in their limbs, were as active as normal rabbits, and had comparable body weights.

In conclusion, there was no change in ED90 (sensitivity) in hypertension, but increased resistance changes per unit change in drug dose by local administration of both dilator and constrictor drugs were similar with all the drugs employed. Our findings are best explained by the hypothesis that hypertrophy of the musculature of the precapillary vessels makes them a nonspecific amplifier of vascular resistance changes evoked by dilator and constrictor stimuli.

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