Increased Resistance and Impaired Maximal Vasodilation in Normotensive Vascular Beds of Rats with Coarctation Hypertension

DAVID R. BELL, M.S. AND HENRY W. OVERBECK, M.D., PH.D.

SUMMARY To study the resistance of normotensive vascular beds in coarctation hypertension, we measured perfusion pressures of pump-perfused (blood), innervated, isolated hindlimbs of 12 rats (Group A) with 4 weeks of hypertension due to partial constriction of the abdominal aorta above the renal arteries, and of three control groups: 11 normotensive rats (Group B) with aorta sham-constricted, nine normotensive rats (Group C) with slight (5%) hindquarters atrophy due to partial constriction of the abdominal aorta below the renal arteries, and six rats with two-kidney, one clip Goldblatt hypertension (Group D). After aortic constriction, measured femoral arterial pressures in Group A rats remained normotensive. In hypertensive rats of Groups A and D, compared to normotensive Group B or C rats, hindlimb pressure-flow curves were displaced toward the pressure axis \( p < 0.05 \). Compared to normotensive rats, drop in hindlimb resistance after acute local nerve section was increased in rats with coarctation hypertension. Residual resistance after maximal vasodilation with intraarterial sodium nitroprusside remained elevated in hypertensive rats of Groups A and D \( p < 0.05 \), as compared to normotensive rats, and compared to Group B rats, this residual resistance in the coarcted rats of Group A was increased by 9%. Thus, in normotensive vascular beds of rats with chronic hypertension caused by aortic coarctation, resistance is elevated. The neurogenic component contributes to this high resistance, and structural vascular changes, indicated by impaired maximal vasodilation, may also contribute to the elevated resistance. It is most unlikely that these resistance changes are attributable to elevated hindlimb intravascular pressures. (Hypertension 1: 78-85, 1979)

KEY WORDS • vascular wall-to-lumen ratio • structural component of resistance • neurogenic component of resistance • limb vascular bed • pressure flow relationship • Goldblatt hypertension • plasma renin concentration

Coarctation hypertension is a useful model for examining the effects of intravascular pressure on vascular structure and function in hypertension, because the vascular beds below the coarctation are not exposed to elevated levels of pressure. Thus, abnormalities observed could not be said to be merely secondary to increased intravascular pressure. We have previously reported increased salt and water content in the walls of arteries from these normotensive vascular beds in rats with coarctation hypertension.1 It has been suggested that such “waterlogging” of arterial walls increases vascular resistance and responses.2 Therefore, it is of considerable interest to investigate the status of vascular resistance in these normotensive beds in coarctation hypertension.

In 1963 Nolla-Panades3 reported increased resting resistance and responses to norepinephrine in the normotensive hindquarters vascular beds of rats with coarctation hypertension. However, his experiments were conducted in hindquarters perfused with Krebs-Henseleit solution with no onotic substitute. Thus, it is possible that the abnormalities in resistance he observed may have been artifacts, due, for example, to interstitial edema of the preparation. More importantly, Nolla-Panades did not document residual resistance at maximal vasodilation; this measurement is considered a prime indicator of the status in hyper-

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tension of structural changes increasing vascular wall-to-lumen ratio. It is especially important to determine if such structural changes occur in resistance vessels in hypertension in the absence of increases in intravascular pressure. For these reasons, we felt Nolla-Panades' experiments should be extended with measurements in blood perfused beds of pressure-flow relationships, and resistance at maximal vasodilation.

Methods

Normotensive male Sprague-Dawley rats approximately 2 months old and weighing 150-200 g were randomly divided into four experimental groups. To create coarctation hypertension in 16 rats (Group A), we placed a partially constricting silver clip (diameter 0.813 mm) around the abdominal aorta upstream to the origin of both main renal arteries. In 21 rats (Group B) a clip (diameter ≥ 1.48 mm) too large to constrict the aorta was similarly placed; this group of rats served as sham-coarcted normotensive controls. In a third group of 15 rats (Group C), a partially constricting clip (diameter 0.610 mm) was placed around the abdominal aorta below the origin of both renal arteries. Because such infra-renal aortic coarctation reduces downstream intravascular pressure and flow but does not produce hypertension, this group of rats served as normotensive controls for any hindquarters atrophy occurring in the rats with coarctation hypertension (Group A). In a final group of nine rats, two-kidney, one clip Goldblatt hypertension was created by partially constricting the left renal artery with a silver clip (diameter 0.406-0.434 mm) with the opposite kidney intact.

Postoperatively, the rats were maintained on a diet of standard rat chow and tap water ad libitum. Systolic arterial blood pressures in the hindquarters of all rats were measured weekly by the tail plethysmographic method under light ether anesthesia.

Four to 5 weeks after surgery, we measured carotid and femoral arterial pressures directly with the rats anesthetized with a partial intravenous injection of sodium pentobarbital (30 mg/kg I.V.). In most of these anesthetized rats (n = 12, 11, 9 and 6 in Groups A, B, C and D, respectively), we then measured perfusion pressure in the vascularly isolated, innervated, pump-perfused hindlimb vascular beds, using the procedure described by LaVerty. Briefly, we isolated one hindlimb from the body by severing and ligating skin and muscle connections and by dislocating the hip from the pelvis with a ligature. The major nerve connections of the limb were left intact and the femoral vein was undisturbed. Respiration was natural. Before pump-perfusion of the limb the rat was given 400 USP units of heparin and a supplemental dose of chloralose and pentobarbital (25 mg/kg and 6 mg/kg I.V., respectively). The pump used was similar to a pump that has been described; this pump provides a nonpulsatile flow, is pressure independent to at least 300 mm Hg, and produces negligible hemolysis. The pump was primed with approximately 2 ml of heparinized blood drawn from a donor rat of the same experimental group as the rat to be perfused.

Then blood from the carotid artery of each rat was pumped at a constant rate of 1 ml/min into the femoral artery of the isolated limb.

The perfusion was continued for 15 minutes to establish a steady state. Perfusion pressure was monitored by a Statham P23Gb pressure transducer and a Hewlett Packard recorder. The pump flow was then adjusted so that steady-state perfusion pressure (minus pressure drop across the tubing and cannula) was similar to the rat's femoral arterial pressure; this pump flow was recorded and designated "resting limb blood flow." "Resting limb vascular resistance" was calculated using this value.

To study pressure-flow relationships in the limb vascular bed, pump flow was then adjusted serially at 5- to 9-minute intervals to 0.125, 0.25, 0.5, 1.0, 1.5, and 2.0 ml/min, in that order. Steady-state perfusion pressures were recorded. Then the flow sequence was repeated and averaged values reported.

Pump flow was again returned to 1 ml/min, and, when a steady state was restored, the femoral and sciatic nerves to the perfused limb were severed. Ten minutes later the steady-state limb perfusion pressure was recorded. Calculated resistance was designated "resistance after acute nerve section." Then a supramaximal dose of sodium nitroprusside (0.15 mg/kg in 0.05-0.10 ml isotonic NaCl solution) was injected rapidly into the pump tubing upstream to the pump. Maximal vasodilation of the limb was tested by successively doubling the dose. In preliminary experiments in three rats, no further vasodilation was elicited by papaverine injections. Perfusion pressure 4 minutes after the final nitroprusside injection was recorded; calculated resistance was designated "resistance after maximal sodium nitroprusside vasodilation."

In all rats the perfusion pressure gradient across the outflow tubing and cannula was measured at each flow rate used; this value was subtracted from the perfusion pressures used to calculate all limb resistances. Limb resistances were calculated as the ratio of perfusion pressure to limb blood flow and expressed in terms of hindlimb wet weight.

After the perfusion study, blood was taken from all animals for measurement of hematocrit. In most animals plasma creatinine, sodium, potassium, calcium and magnesium concentrations were also measured. Plasma creatinine concentration was measured by auto-analyzer, plasma sodium and potassium concentrations by flame photometer (Beckman), and calcium and magnesium concentrations by atomic absorption spectrometry (Perkin-Elmer). Each rat was autopsied to verify clip type, placement, and general health. Kidneys and heart were weighed. Hindlimbs were removed and both wet and dry (after oven drying at 86°C for 7 days) weights obtained.

Thirteen additional rats of Groups A and B each were prepared. Four to 5 weeks after clipping, these rats were decapitated without anesthesia and aortic blood was collected for the first 2 seconds. Plasma renin concentrations were measured by radioimmunoassay.
Among groups, variables were compared with one-way analysis of variance and, if this indicated that significant differences existed, means were then compared with Student-Newman-Kuels test. Student’s t test for paired replicates was used for within-group comparisons. Entire pressure-flow curves were also assessed with profile analysis. The null hypothesis was rejected at \( p \leq 0.05 \).

### Results

All rats reported remained healthy with no evidence of cardiac or renal insufficiency or malignant hypertension at the time of study. At this time body weights (table 1) and serum sodium, potassium, calcium, magnesium and creatinine concentrations did not differ significantly among the experimental groups and were within normal limits. Hematocrits, also obtained after the perfusions, were within normal ranges.

Changes occurred in kidney, heart and limb weights in these rats (table 1). Absolute left kidney weight, as well as ratio of left kidney weight to body weight, were slightly (11%) but significantly (\( p < 0.05 \)) reduced in rats with coarctation hypertension (Group A) compared to sham-coarcted controls (Group B). In the Goldblatt hypertensive rats (Group D) absolute weight of the clipped left kidney, as well as ratio of left kidney weight to body weight, were decreased by 27% (\( p < 0.05 \)), whereas the weight of the untouched right kidney, and its ratio to body weight, increased by 19% (\( p < 0.01 \)). Absolute heart weight and heart weight expressed in terms of body weight increased by 44 and 21%, respectively (\( p < 0.01 \)) in rats with coarctation and Goldblatt hypertension (Groups A and D), compared to sham-coarcted normotensive control rats of Group B. There was also a slight (1%), but significant (\( p < 0.01 \)), increase in heart weight/body weight in normotensive rats with aorta coarcted below the renal arteries (Group C). Hindlimb wet weight, expressed in terms of body weight (table 1), was reduced 6 and 5%, respectively (\( p < 0.01 \)) in rats of Groups A and C with partially constricted aortas compared to sham-coarcted control rats of Group B, suggesting that aortic constriction produced slight hindlimb atrophy.

As figure 1 indicates, tail systolic blood pressures measured indirectly under light ether anesthesia each week for the 3 weeks after clipping remained unchanged in rats with coarction hypertension (Group A) and in normotensive sham-coarcted controls (Group B), dropped significantly in rats with aortas coarcted below the renal arteries (Group C) and increased significantly in rats with Goldblatt hypertension (Group D). Mean carotid arterial pressure directly measured at the time of the perfusion study under light chloralose anesthesia was significantly increased in rats with coarctation and Goldblatt hypertension (Groups A and D) as compared to both normotensive control groups (fig. 2). As indicated by figure 2 and table 2, mean, systolic, and diastolic femoral arterial pressures in rats with coarctation hypertension (Group A) did not differ significantly from those in the normotensive controls of Group B, remaining within normal limits. Pulse pressure, however, decreased slightly in the femoral arteries of the Group A rats. Mean, systolic, and diastolic femoral arterial pressures of rats with aortas coarcted below the renal arteries (Group C) were significantly decreased and those of Goldblatt hypertensive rats (Group D) were significantly increased compared to

### Table 1. Body and Organ Weights*

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
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<tbody>
<tr>
<td></td>
<td>(Coarctation</td>
<td>(Sham coarctation)</td>
<td>(Infra-renal coarctation)</td>
<td>(Goldblatt hypertension)</td>
</tr>
<tr>
<td>Body wt. (g)</td>
<td>353 ± 5(16)</td>
<td>353 ± 3(21)</td>
<td>359 ± 4(15)</td>
<td>359 ± 10(9)</td>
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<tr>
<td>Lt. kidney wt. (g)</td>
<td>1.154 ± 0.044(16)§</td>
<td>1.323 ± 0.037(21)</td>
<td>1.326 ± 0.040(15)</td>
<td>0.984 ± 0.106(9)‡</td>
</tr>
<tr>
<td>Lt. kidney wt./body wt.</td>
<td>33 ± 1(16)§</td>
<td>37 ± 1(21)</td>
<td>37 ± 1(15)</td>
<td>27 ± 3(9)§</td>
</tr>
<tr>
<td>Rt. kidney wt. (g)</td>
<td>1.198 ± 0.056(16)</td>
<td>1.308 ± 0.044(21)</td>
<td>1.331 ± 0.050(15)</td>
<td>1.554 ± 0.062(9)§</td>
</tr>
<tr>
<td>Rt. kidney wt./body wt.</td>
<td>34 ± 1(18)</td>
<td>37 ± 1(21)</td>
<td>37 ± 1(15)</td>
<td>44 ± 3(9)§</td>
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<tr>
<td>Heart weight (g)</td>
<td>1.604 ± 0.050(16)§</td>
<td>1.176 ± 0.022(21)</td>
<td>1.267 ± 0.022(15)</td>
<td>1.446 ± 0.048(9)§</td>
</tr>
<tr>
<td>Heart wt./body wt.</td>
<td>481 ± 15(16)§</td>
<td>333 ± 6(21)</td>
<td>337 ± 7(15)§</td>
<td>403 ± 14(9)§</td>
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<tr>
<td>Perfused hindlimb wt.</td>
<td>20.107 ± 0.244(14)</td>
<td>20.754 ± 0.234(20)</td>
<td>20.266 ± 0.287(15)</td>
<td>21.206 ± 0.589(9)</td>
</tr>
<tr>
<td>Perfused hindlimb/body</td>
<td>574 ± 10(14)</td>
<td>588 ± 6(20)</td>
<td>565 ± 7(15)</td>
<td>592 ± 10(9)</td>
</tr>
<tr>
<td>Opposite hindlimb wt.</td>
<td>19.221 ± 0.297(14)</td>
<td>20.597 ± 0.217(20)</td>
<td>19.825 ± 0.289(15)</td>
<td>20.701 ± 0.590(9)</td>
</tr>
<tr>
<td>Opposite hindlimb/body</td>
<td>548 ± 10(14)§</td>
<td>583 ± 6(20)</td>
<td>552 ± 5(15)§</td>
<td>578 ± 7(9)§</td>
</tr>
<tr>
<td>Perfused hindlimb dry wt.</td>
<td>6.105 ± 0.131(16)</td>
<td>6.509 ± 0.084(21)</td>
<td>6.365 ± 0.129(15)</td>
<td>6.380 ± 0.193(9)</td>
</tr>
<tr>
<td>Opposite hindlimb dry wt.</td>
<td>6.248 ± 0.141(16)</td>
<td>6.865 ± 0.087(21)</td>
<td>6.375 ± 0.110(15)</td>
<td>6.602 ± 0.225(9)</td>
</tr>
</tbody>
</table>

*Means ± SEM; Numbers of observations in parenthesis.
†Wet weights.
‡\( p < 0.05 \), compared to Group B.
§\( p < 0.01 \), compared to Group B.
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200 150 100 50

Group D

Group C

P<.05, vs Group B

t

Clipping

Weeks Postoperative

FIGURE 1. Mean (±SEM) tail systolic arterial pressures (by plethysmography) recorded at weekly intervals following clipping. Groups are identified on figure. Asterisk represents pressures significantly different (p < 0.05) from those in sham-coarcted control rats of Group B.

200 150 100 50

CBP FBP

Group A

Group B

Group C

Group D

FIGURE 2. Mean (±SEM) carotid (CBP) and femoral (FBP) arterial pressures measured directly under light chloralose anesthesia 4 weeks after clipping. The p values are represented for comparison with pressures in the sham-coarcted control rats of Group B.

Table 2. Femoral Arterial Pressures*

<table>
<thead>
<tr>
<th></th>
<th>Group A (Coarctation hypertension)</th>
<th>Group B (Sham coarctation)</th>
<th>Group C (Infra-renal coarctation)</th>
<th>Group D (Goldblatt hypertension)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic (mm Hg)</td>
<td>116 ± 5 (13)</td>
<td>110 ± 2 (20)</td>
<td>78 ± 3 (13)</td>
<td>156 ± 11 (9)</td>
</tr>
<tr>
<td>Diastolic (mm Hg)</td>
<td>105 ± 5 (13)</td>
<td>95 ± 3 (20)</td>
<td>72 ± 3 (13)</td>
<td>138 ± 12 (9)</td>
</tr>
<tr>
<td>Pulse (mm Hg)</td>
<td>11 ± 1 (13)</td>
<td>15 ± 1 (20)</td>
<td>6 ± 1 (13)</td>
<td>18 ± 1 (9)</td>
</tr>
</tbody>
</table>

*Means ± SEM; numbers of observations in parentheses; mean pressures provided in figure 2.
†p < 0.05, compared to Group B.
‡p < 0.01, compared to Group B.

We measured resting limb blood flow by setting perfusion pressure equal to femoral arterial pressure in each rat and then measuring pump flow (fig. 3). Compared to sham-coarcted rats of Group B, resting limb blood flow per gram limb wet weight was reduced by 29% (p < 0.05) in rats with coarctation hypertension (Group A) and by 17% (p < 0.05) in rats with aortas coarcted below the renal arteries (Group C). A trend toward reduced limb flow in rats with Goldblatt hypertension (Group D) was not statistically significant (p > 0.05). Compared to normotensive sham-coarcted controls of Group B, resting limb vascular resistance calculated from these flows, was elevated by 57 and 67%, respectively (p < 0.01) in rats with coarctation and Goldblatt hypertension (Groups A and D). In contrast, resting limb vascular resistance was reduced by 28% (p < 0.01) in rats with aortas partially constricted below the renal arteries (Group C).

Limb pressure-flow curves are presented in figure 4. Analysis of variance revealed that at nearly all flows significantly higher pressures (and therefore resistances) were induced in rats with coarctation and Goldblatt hypertension (Groups A and D) compared to normotensive control rats of Groups B or C (p < 0.05). In contrast, at flows > 1 ml/min, significantly lower pressures and resistances were evoked in rats with aortas coarcted below the renal arteries (Group C) compared to sham-coarcted normotensive control rats of Group B (p < 0.01). These conclusions were supported by profile analysis.10 Limb resistances at pump flows of 1 ml/min are presented in figure 5, indicating that at this flow rate resistance was elevated by 40% and 69% in hypertensive rats of Groups A and D, respectively, and reduced by 39% in normotensive rats with aortas coarcted below the renal arteries (Group C).

Acute nerve section dropped hindlimb resistance in all rats studied. The magnitude of this drop, however, differed among the groups. Expressed as percentage of resting resistance with nerves intact, the decrease in resistance evoked by nerve section (mean ± SEM) was 43.1 ± 2.8, 26.8 ± 3.6, 19.1 ± 1.7 and 30.8 ± 4.1% in Groups A, B, C and D, respectively. This drop in resistance was greater in Group A (p < 0.01) than in
Group A Group B Group C Group D

Figure 3. Resting limb blood flow (ml/min/g limb wet weight). Pump perfusion pressure set to equal femoral arterial pressure. Groups are identified on the figure. The \( p \) values are represented for comparison with flows in the sham-coarcted control rats of Group B.

Figure 4. Pressure-flow relationships in the isolated innervated, pump-perfused vascular bed of the hindlimb. Groups are identified on the figure. The checks represent \( p \) values for comparison of points for Groups A (coarctation hypertension) and C (aortas coarcted below renal arteries). The asterisks represent \( p \) values for comparison of values in Groups A and B (sham-coarctation).
after maximal vasodilation was elevated by 9% ($p < 0.05$) in rats with coarctation hypertension (Group A), and by 32% ($p < 0.01$) in rats with Goldblatt hypertension (Group D). The difference between Groups A and D was highly significant ($p < 0.01$). In contrast, residual resistance was decreased by 27% ($p < 0.01$) in Group C rats with aortas coarcted below the renal arteries. Again, the difference between Groups A and C was highly significant ($p < 0.01$).

Plasma renin concentrations in rats with coarctation hypertension (Group A) were increased by 81% ($p < 0.001$) to 21.8 ± 2.0 ng angiotensin I/ml/hr, as compared to 12.1 ± 0.8 in sham-coarcted normotensive control rats (Group B).

**Discussion**

Abnormalities in vascular wall composition, structure, and function occur in hypertension, but it is often difficult to determine whether these changes reflect underlying causative mechanisms or, on the other hand, are simply the result of the increased intravascular pressure. Experimentally induced coarctation hypertension may be used to examine the effects of intravascular pressure on vascular structure and function in hypertension, because the vascular beds below the coarctation are not exposed to elevated levels of pressure. In rats with this model of hypertension we found "waterlogging" in the walls of arteries from normotensive vascular beds. Furthermore, Nolla-Panades, using a preparation similar to that of the present study, but perfused with artificial solution rather than blood, showed that resistance is elevated and norepinephrine responses are enhanced in the normotensive vascular bed of the hindquarters in coarcted rats.

The results of the present investigation in blood-perfused hindlimbs of rats with coarctation hypertension confirm and extend Nolla-Panades' observations by indicating that resistance is elevated over a wide range of flows, that the major component of this elevated resistance is related to neural influences, and that a significant portion of the elevated resistance persists after maximal chemical vasodilation, suggesting that vascular structural changes have occurred.

Both we and Nolla-Panades repeatedly measured hindquarters arterial pressures in these rats and never found them to exceed those in sham-coarcted normotensive control rats. However, continuous intra-arterial pressures over the entire experimental period were not obtained, so there remains the remote possibility that there were slight transient pressure elevations. Nevertheless, it is most unlikely that these

![Figure 5](https://hyper.ahajournals.org/)

**Figure 5.** Limb vascular resistances, mm Hg/ml flow min⁻¹ per gram limb wet weight, with pump flow at 1 ml/min. Groups are identified on the figure. Clear bars represent resistance of intact limbs; crosshatched bars represent resistance 10 minutes after acute section of nerves supplying the limb; solid bars represent resistance after maximal vasodilation with sodium nitroprusside. The p values are represented for comparison with resistances in the sham-coarcted control rats of Group B.
observed abnormalities in resistance are the direct
effects of elevated arterial pressures. Nor may it be
argued that these hypertensive rats had elevated hind-
quarters blood flows, with resistance changes result-
ing from "long-term autoregulation"; hindlimb
blood flow was actually reduced. The changes we have
observed in the present study cannot be artifacts
caused by perfusion with artificial media. Nor can
they be explained on the basis of hindquarters atrophy
with decreased numbers of perfused vessels, because
there was similar hindquarters atrophy in the normo-
tensive rats with aortas coarcted below the renal
arteries (Group C). In these latter control rats, rest-
ing hindlimb resistance was reduced, as was resistance
after maximal sodium nitroprusside vasodilation,
changes in the opposite direction from those we
observed in the rats with coarctation hypertension.
Indeed, findings in this control group of rats increase
the significance of the changes in resistance we
observed in the rats with coarctation hypertension.

Figure 5 may be useful in analyzing the components
of the elevated resistance in the normotensive hind-
lims of these rats with coarctation hypertension
(Group A). It may be seen that acute local nerve sec-
tion evoked a greater (p < 0.01) fall in limb resistance
in these rats than in the sham-coarcted normotensive
control rats (Group B), reducing resistance to levels
not significantly different from those in the sham-
coarcted rats. These data suggest that the component
of resistance related to neural influences, the
"neurogenic" component, accounts for the major por-
tion of the elevated resistance of the hindlimb in the
rats with coarctation hypertension. However, it cannot
be said whether increased nerve traffic, modula-
tion of nerve traffic by angiotensin, increased vessel
responsiveness (on a structural and/or functional
basis), or a combination, contributes to this elevated
"neurogenic" component of resistance.

In contrast, the "humoral-myogenic" component of
resistance (the difference between resistance after
nerve section and resistance at maximal vasodilation
expressed as percentage of resting resistance) was, if
anything, reduced in the rats with coarctation hyper-
tension. This finding suggests that the increased
plasma angiotensin levels in the hypertensive rats with
aortic coarctation did not directly contribute to the
rise in limb resistance. Plasma renin activity was not
measured in the rats with Goldblatt hypertension, so
we are unable to comment on the contribution of
angiotensin to the elevated hindlimb resistance in this
form of hypertension.

The slightly but significantly greater magnitude of
perfusion pressure, and, therefore, of residual
resistance after maximal sodium nitroprusside vaso-
dilation (the "structural" component of resistance) we
observed in the hindlimbs of these rats with coarcta-
tion hypertension is especially intriguing. It is unlikely
that this elevated residual resistance can be explained
on the basis of increased passive vasoconstriction,
because hindlimb perfusion pressure, and therefore
transmural distending pressure, was higher in the rats
with coarctation hypertension. This observation of im-
paired maximal vasodilation, in conjunction with the
hyperresponsiveness to norepinephrine observed by
Nolla-Panades, suggests that structural changes in-
creasing wall-to-lumen ratio may have occurred in
vessels of these hypertensive rats in the absence of in-
creases in intravascular pressure or flow. Such struc-
tural changes in vessels in hypertension have been felt
to be almost exclusively, if not exclusively, the result
of elevated intravascular pressure or flow. This is
because there is evidence that the magnitude of such
wall thickening is directly proportional to the level of
intravascular pressure. It has also been observed
that such thickening may be prevented if the vascular
bed is "protected" from the elevated arterial pressure
by arterial ligation. Furthermore, there is evidence
that vascular structural changes, once present, may
regress if blood pressure is returned to normal
levels. In the present investigation, the increase in
this "structural" component of resistance was far
greater in the Goldblatt than in the coarctation hyper-
tensive rats, presumably reflecting the important
causal role of elevated intravascular pressure.

On the other hand, there are also observations
suggesting that additional factors may act in concert
with intravascular pressure to produce structural
changes in the vascular system in hypertension. For
example, there is chemical evidence for structural
vascular changes in young rats of the spontaneously
hypertensive strain (SHR) before blood pressure
rises. Folkow and co-investigators have reviewed
hemodynamic evidence suggesting that SHR may
have a predisposition for vascular and cardiac wall
thickening.

Assuming that the impaired maximal vasodilation
we have observed, and the hyperresponsiveness Nolla-
Panades observed, in the hindquarters of rats with
coarctation hypertension does in fact reflect increases
in vascular wall-to-lumen ratio, these structural
changes can be attributed either to a genetic
predisposition or to significant elevations in intra-
vascular pressure. Instead they must be explained on
the basis of abnormal neural or humoral stimuli. It
has been suggested that adrenergic neurons may exert
a trophic influence on vascular smooth muscle. Exposure
to elevated levels of renin-angiotensin-aldoste-
one or other humoral factors might in some
way alter the composition of vessel walls to increase
wall-to-lumen ratio. Clearly, the influence of such
systemic factors must be explored further.

The identification of factors other than pressure
playing a role in the development of vascular struc-
tural changes in hypertension is most important,
because it will provide additional insight into disease
mechanisms and may eventually offer new therapeutic
approaches.

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