Transient and Persistent Changes in Rabbit Blood Vessels Associated with Maintained Elevation in Arterial Pressure

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SUMMARY Arteries and veins of hypertensive rabbits were examined 8 weeks after partially constricting the abdominal aorta above both kidneys, and compared with those from sham-operated animals. Structural and functional changes in blood vessels after 2 weeks, when the arterial pressure first attained a new elevated level, have been described previously, and are now compared with changes 6 weeks later. The increase in blood vessel mass could be correlated with an increase in deoxyribonucleic acid (DNA) content. In contrast to the status at 2 weeks postoperatively, there was no increased uptake of ³H-thymidine, ³H-proline, or ³H-lysine at 2 months. Furthermore, at this time cell nuclei labeled with ³H-thymidine were infrequent. Some vessels showed evidence of change in the physical characteristics of their wall. Only minimal changes were observed in those parameters of adrenergic nerve function measured — neuronal ³H-norepinephrine uptake and vessel wall catecholamine content — that had been markedly changed at 2 weeks. The results of this work, together with those of other studies of this model, suggest two phases of response of the arterial wall to pressure rise: an initial dynamic proliferative cellular response mainly of vascular smooth muscle associated with changes in adrenergic neuronal parameters, and a subsequent equilibrium phase characterized by an increased number of smooth muscle cells, some changes in the extracellular components, and minimal changes in the adrenergic innervation. (Hypertension 2: 63-72, 1980)

KEY WORDS • smooth muscle • artery wall • adrenergic innervation • PAAC rabbit • blood pressure • hypertension • abdominal aorta constriction • norepinephrine • cellular proliferation

PREVIOUS studies have defined some structural and functional changes in the walls of arteries and veins of the rabbit with partial abdominal aorta constriction (PAAC) above both kidneys.²⁷ Two weeks postoperatively when the arterial pressure in the vascular arterial compartment proximal to the constriction had reached a new plateau, arteries were thicker and longer. In such vessels, vascular smooth muscle proliferation and an increase in amino acid uptake with incorporation into the vessel wall were associated with an increase in the number of vascular smooth muscle cells. Venous smooth muscle was hypersensitive to norepinephrine (NE). All of these changes could be correlated with the level of arterial pressure. There was also evidence of altered adrenergic nerve terminal function in the wall of the hypertensive arteries. It is proposed that some of these changes are secondary to local rise in intravascular pressure.⁶

Since these observations were made when active changes were still taking place in the vessel wall, it was deemed important to determine which if any of these changes persisted when the arterial pressure remained at an elevated but stable level. With this in mind, a study of some of the structural and functional features of the blood vessel wall was undertaken 8 weeks after constriction. At this time, the arterial pressure had remained elevated at a new level for about 6 weeks.

Answers to two questions were sought in this study: 1) Are the measured tissue parameters related to the level of the arterial pressure? and 2) Do the changes in blood pressure parameters 8 weeks after constriction differ in relation to arterial pressure from those previously found at 2 weeks? A preliminary report has been published previously.⁸
Methods

Many types of measurements were made on each animal. Because of limitation in the amount of available tissue, not all measurements could be made on each anatomical vessel. Hence, a spectrum of vessels was utilized.

Induction of Hypertension

The method of inducing hypertension in New Zealand white rabbits was essentially the same as that previously described. A ligature placed around the abdominal aorta between the celiac and anterior mesenteric artery was tightened sufficiently to halve mean femoral artery pressure. Some rabbits received sham operations in which a ligature was placed loosely around the abdominal aorta. Approximately 8 weeks later, after arterial pressures were recorded during barbiturate anesthesia and 6 ml of arterial blood had been taken for estimation of plasma renin activity, the rabbits were bled, and the thoracic and abdominal aorta, basilar, brachial, common carotid, ear, renal and saphenous arteries, and the cephalic, portal and saphenous veins, and also the heart and both kidneys, were removed.

Vessel Dimensions and Wet Weight

As vessels are known to increase their length, wall thickness, and weight in this model of hypertension, specimen length was defined by two fixed anatomical landmarks, where possible: the common carotid artery, between the upper border of the first rib and its bifurcation; the thoracic aorta, from the origin of the left subclavian artery to the aortic hiatus of the diaphragm; the abdominal aorta from the level of the left renal artery to its bifurcation; the thoracic aorta, from their origin to subdivision; the brachial arteries from between the levels of the shoulder and elbow joints; the saphenous artery from its origin from the femoral artery to the level of the knee joint; and the portal vein from the confluence of the main mesenteric veins to its prehepatic branching. Where this was not possible, constant length segments of ear artery and cephalic and saphenous veins were removed. The dimensions of excised vessels were determined in vitro. Unstretched vessel length was measured using a caliper and ruler. Total weight of vessel was obtained after preparations had been wiped in a standard manner on a tile. Portions of these vessels were placed for 1 hour in cold Krebs-bicarbonate solution containing phenoxybenzamine (10⁻⁴ M) and xylocaine (10⁻⁴ M) to minimize intrinsic muscle tone and the development of spasm during cleaning and cutting longitudinally. Wall thickness and internal circumference were measured using a microscopic technique. Kidney and heart weights were obtained.

DNA Determinations

Arteries were weighed, frozen, and treated by a modification of the method developed by Zamenhof et al., and described by Bevan.

Tritiated Thymidine Uptake and Autoradiography

Segments of arteries and veins were utilized to study DNA synthesis by ³H-thymidine (³H-Tdr) uptake and autoradiography. Hypertensive vessels and sham-operated control arteries were attached to plastic holders and submerged in a jacketed tissue bath (37°C) containing 50 ml of physiological salt solution bubbled with 95% O₂ and 5% CO₂. Tissues were equilibrated for 1 hour, and then ³H-Tdr (Sa 2.0 Ci/mmole, New England Nuclear) was added to the bath to make a concentration of 2 μCi/ml. After 20 minutes' incubation, the tissues were rinsed with physiological salt solution at 37°C and washed for 20 minutes with two further rinses. Tissues were divided, one portion was blotted with filter paper, weighed, digested, and its radioactivity determined using a Nuclear-Chicago Mark II scintillation counter. The ³H-Tdr uptake was expressed as milliliters of bath solution cleared per gram wet weight of tissue, i.e., tissue/medium ratio. The other portion of each vessel was fixed in 10% formaldehyde, dehydrated, embedded in paraffin, sectioned at 5 μ, and processed for autoradiography by the method of Kopriwa and LeBlond.

Amino Acid Incorporation

Segments of vessels to be studied were placed in a solution of either 1-proline, 2.3-³H (0.04 μg/ml; 10 μCi/ml) or 1-lysine 4.5-³H (0.05 μg/ml; 10 μCi/ml) in Krebs-bicarbonate bubbled with 95% O₂ and 5% CO₂ at 37°C for 3 hours. Tissues were subsequently rinsed in three changes of plain unbubbled Krebs-bicarbonate at 4°C for 18 hours, blotted dry, and weighed.

Tritiated Norepinephrine Uptake

To determine tritiated norepinephrine (NE) uptake, essentially the same method was used as described previously. Paired adjacent segments of each vascular specimen were equilibrated in Krebs-bicarbonate solution at 38°C and bubbled with 95% O₂ and 5% CO₂ for 90 minutes. During the last 30 minutes of the equilibration period, one segment of each paired specimen was treated with cocaine (10⁻⁴ M) to block neuronal uptake. Both the cocaine-treated and the control segments were then soaked in I-7¹H-NE hydrochloride (10⁻⁴ M) for 60 minutes. After a rapid rinse, the tissues were blotted, weighed, and their lengths measured on a calibrated microscope slide; the tissues were then digested. Tissue radioactivity was measured by scintillation spectrometry, and uptake was expressed as milliliters of bath fluid cleared per millimeter length of wet tissue.

Norepinephrine Content

After being blotted with filter paper, the tissues were weighed and homogenized in 5% trichloroacetic acid with a Willens Polytron homogenizer. After centrifugation, the supernatant fluid was neutralized to pH 8.4 in the presence of alumina, and the latter was
eters of adrenergic neuronal function were increased in the vessel wall in this animal model consequent upon a hypersensitivity of the venous smooth muscle to NE.

neurons, are transient and do not persist even when a rise in pressure, such as changes in the adrenergic nervous system, are related to the level of the arterial pressure. Where relevant, differences between this study and that carried out at 2 weeks are described below. Details are shown in tables 1 and 2.

**General Data**

Mean carotid and femoral artery pressures of the aorta-constricted animals at 8 weeks were 140.60 ± 4.62 and 100.60 ± 4.99 respectively (mean ± standard error: number of animals). These values were significantly different from each other and were not different from the mean values of operated animal groups 2 weeks after surgery. Mean carotid and femoral artery pressures of the sham-operated animals were 105 ± 2.2 and 104 ± 2.4 respectively.

Preoperative body weights were 2.2 ± 0.14 and 2.17 ± 0.16 kg for operated and sham groups respectively; the same groups at sacrifice were 3.48 ± 0.05 and 3.34 ± 0.16 kg.

**Heart and Kidneys**

In all hypertensive animals, the heart was enlarged; left ventricular hypertrophy was marked. There was good correlation between heart weight and carotid artery pressure: \( r = 0.79 \) for the 2-weeks and 0.82 for the 8-weeks animals. The relationship between these two parameters was not significantly different at the two time points (fig. 1). Kidney weights were independent of arterial pressure and did not significantly change between 2 and 8 weeks; macroscopically, the kidneys appeared normal.

**Arteries and Veins: Weight and Dimensions**

In the 8-week hypertensive animals, weights of the anatomically defined thoracic aorta and common carotid, but not the ear artery, could be positively correlated with arterial pressure: \( r = 0.80 \) (0.35 to 0.95), 0.61 (0.05 to 0.87), and 0.40 (±0.80 to −0.30) respectively. Ranges refer to 95% confidence limits of correlation coefficient. There was no difference in the relationship between weight of thoracic aorta and common carotid artery at 2 and 8 weeks and arterial pressure. However, the mean weight per unit length of the ear artery was significantly greater in the hypertensive animals compared with their matched controls. This same parameter in saphenous and renal arteries from the distal normotensive circulation segment and the cephalic and saphenous veins showed no tendency to rise with arterial pressure increase: the mean paired values for the operated and sham groups were not different. The apparent exception to this lack of change in arteries from the distal circulation was the abdominal aorta weight, which correlated positively with carotid artery pressure: \( r = 0.58 \) (0.04−0.80).

The relationship between wall thickness of isolated carotid and ear arteries and arterial pressure showed a
### TABLE 1. Values of Various Parameters of Blood Vessels of Rabbits 8 Weeks after Partial Abdominal Aortic Constriction and Their Sham-Operated Controls

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Weight (mg)</th>
<th>Thickness (mm)</th>
<th>( ^{3} \text{H}-\text{Thymidine uptake} ) (ml/g)</th>
<th>DNA content (ng/vessel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>7995±1180</td>
<td>12010±220</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left kidney</td>
<td>8200±330</td>
<td>7960±110</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right kidney</td>
<td>8210±240</td>
<td>7980±100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoracicorta</td>
<td>425.2±414</td>
<td>508.7±414</td>
<td>0.349±0.045</td>
<td>0.451±0.05</td>
</tr>
<tr>
<td>Abdom.orta</td>
<td>137.2±8.8</td>
<td>164±8.8</td>
<td>0.380±0.03</td>
<td>0.401±0.04</td>
</tr>
<tr>
<td>Carotid artery</td>
<td>50.84±2.88</td>
<td>60.34±3.84</td>
<td>0.348±0.014</td>
<td>0.334±0.016</td>
</tr>
<tr>
<td>Ear artery</td>
<td>0.46±0.028</td>
<td>0.520±0.024</td>
<td>0.368±0.019</td>
<td>0.355±0.018</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>0.138±0.012</td>
<td>0.182±0.01</td>
<td>0.012±0.011</td>
<td>0.01±0.01</td>
</tr>
<tr>
<td>Saphenous artery</td>
<td>0.316±0.0386</td>
<td>0.333±0.023</td>
<td>0.333±0.02</td>
<td>0.361±0.01</td>
</tr>
<tr>
<td>Renal artery</td>
<td>0.014±0.0049</td>
<td>0.911±0.049</td>
<td>0.329±0.02</td>
<td>0.355±0.018</td>
</tr>
<tr>
<td>Cephalic vein</td>
<td>0.298±0.0252</td>
<td>0.295±0.01</td>
<td>0.298±0.02</td>
<td>0.258±0.034</td>
</tr>
<tr>
<td>Saphenous vein</td>
<td>0.492±0.029</td>
<td>0.468±0.009</td>
<td>0.492±0.029</td>
<td>0.468±0.009</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard errors for sham-operated (C) and hypertensive rabbits (H) respectively; \( t \) and \( p \) values refer to paired comparisons of these two groups. In most instances \( n = 5 \), although it varied between 3 and 6. For details of units see text.

* per millimeter vessel length.
† Insufficient paired values for statistics.
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Proline uptake (ml/g)</th>
<th>Lysine uptake (ml/g)</th>
<th>NE content (μg/vessel)</th>
<th>Neuronal uptake TH-NE (ml/g/min)</th>
<th>Median effective NE dose (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.800</td>
<td>0.560</td>
<td>1.54</td>
<td>1.60</td>
<td>0.67</td>
</tr>
<tr>
<td>±0.123</td>
<td>±0.129</td>
<td>±0.37</td>
<td>±0.22</td>
<td>±0.05</td>
</tr>
<tr>
<td>t=1.88:p&lt;0.12</td>
<td>t=1.80:p&lt;0.13</td>
<td>t=0.32:0.86</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 0.9       | 1.10      | 1.77      | 1.60      | 0.800     | 0.560     | 0.12:0.72 |  
| ±0.13     | ±0.10     | ±0.3      | ±0.22     | ±0.12:0.72| ±0.10     | ±0.12:0.72|  
| t=0.50:p<0.04 | t=1.60:p<0.17 |  

| 1.24      | 1.44      | 1.50      | 2.16      | 1.42      | 1.51      | 14.42     | 15.16     | 1.87      | 2.11      | 0.19:0.14 |
| ±0.22     | ±0.17     | ±0.23     | ±0.18     | ±0.50:0.17| ±0.23     | ±0.18     | ±0.50:0.17|  
| t=1.38:p<0.034 | t=1.05:p<0.035 |  

| 2.36      | 2.32      | 2.68      | 3.84      | 11.60     | 14.21     | 2.29      | 1.84      | ±0.63:0.025|  
| ±0.17     | ±0.42     | ±0.84     | ±0.58     | ±0.20:0.13| ±0.26:0.11| ±0.58:0.13| ±0.20:0.13|  
| t=2.06:p<0.13 | t=2.26:p<0.11 |  

| 0.62      | 1.23      | 0.87      | 1.90      | 11.41     | 10.20     | 0.91      | 0.52      | ±0.41:0.17 |  
| ±0.11     | ±0.03     | ±0.15     | ±0.21     | ±0.91     | ±0.52     | ±0.41:0.17| ±0.91:0.52|  
| t=1.24:p<0.030 | t=1.05:p<0.02 |  

| 0.92      | 1.10      | 1.48      | 1.95      | 2.05:0.10 | 1.85:0.16 | 1.43      | 1.5       | ±0.41:0.17 |  
| ±0.16     | ±0.18     | ±0.11     | ±0.21     | ±0.41:0.17| ±0.41:0.17| ±0.41:0.17| ±0.41:0.17|  
| t=2.10:p<0.010 | t=1.85:p<0.016 |  

| 1.45      | 1.37      | 2.28      | 1.60      | 5.33      | 6.80      | 0.32      | 0.36      | ±0.31:0.25 |  
| ±0.58     | ±0.23     | ±0.33     | ±0.32     | ±1.85     | ±2.06     | ±0.04     | ±0.08     | ±0.31:0.25 |  
| t=1.81:p<0.013 | t=0.41:p<0.7 |  

| 1.43      | 1.5       | 2.07      | 1.73      | 11.27     | 11.65     | 0.24      | 0.36      | ±0.31:0.25 |  
| ±0.42     | ±0.21     | ±0.26     | ±0.38     | ±1.23     | ±0.87     | ±0.05     | ±0.08     | ±0.31:0.25 |  
| t=1.36:p<0.25 | t=1.36:p<0.25 |  

| 0.078     | 0.077     | ±0.007    | ±0.013    | ±0.58:0.43|  
|  
|  

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negative trend: \( r = -0.35 \) (−0.78 to +0.3) and −0.51 (−0.85 to +0.2) respectively. The data for the ear artery are shown in figure 2. In contrast, at 2 weeks, wall thickness of all vessels above the constriction increased with rise in arterial pressure. For both the carotid and ear arteries the slopes of the linear regression lines at 2 and 8 weeks were different from each other. The thickness of the thoracic aorta did not vary with the level of the arterial pressure, yet that of the basilar artery increased significantly and to the same extent as at 2 weeks (fig. 2). The thickness of vessels below the ligature, the abdominal aorta and the saphenous and renal arteries, were unrelated to the brachial artery pressure.

**Cellular Division and Protein Synthesis**

In the PAAC rabbit 2 weeks after ligation there was unequivocal evidence of smooth muscle cell proliferation.\(^6\) At 8 weeks, we observed no smooth muscle cell mitoses and only infrequent \(^3\)H-thymidine-labeled nuclei. The \(^3\)H-thymidine, proline, and lysine uptake in all tested vessels was independent of arterial pressure (figs. 3, 4, table 2), and mean uptakes of these labeled compounds from hypertensive and sham-operated controls were obtained from previous studies by Bevan et al.\(^3\)
operated animals were not different from each other (table 1). The only exception to this general statement is the incorporation of lysine into the saphenous artery, when this was significantly higher in the vessels from hypertensive animals. This uptake could not be correlated with either carotid or femoral arterial pressure.

The DNA content of both the thoracic aorta and common carotid artery could be positively correlated with the arterial pressure (fig. 5). The DNA measurements were not performed on the abdominal aorta. Although the regression line for the 8-week hypertensive animals lay above that for the 2-week group, there was no significant difference between their slopes or corrected means. When expressed on a wet weight basis, DNA content was independent of pressure, and there was no difference in the means of hypertensive and control animals by paired comparison at 2 and 8 weeks.

Adrenergic Innervation and Function

As can be seen in tables 1 and 2, the 8-week hypertensive animals exhibited only minimal evidence of change in parameters of adrenergic neuroeffector function. The $^3$H-NE uptake into the adrenergic neurons (cocaine-sensitive uptake) was measured in the carotid, ear, and saphenous arteries and the saphenous and cephalic veins. Only in the ear artery was there a positive correlation between arterial pressure and $^3$H-NE uptake ($r = 0.65 \pm 0.04 - 0.9$), as shown in table 2. There was significant difference between the mean uptakes of the hypertensive and normotensive animals (table 1), but the differences were small; the mean paired increase was 15%.

The median effective concentration of 1-NE obtained in the presence of desmethylimipramine ($10^{-7} M$) for both saphenous and cephalic veins was similar in the control and hypertensive groups.

Plasma Renin Activity

At 8 weeks after constriction, plasma renin activity was low in the hypertensive rabbits in comparison to their matched controls. Mean plasma renin activity values in ng/ml/3 hr for control animals was 75.4 ± 8.32 and for hypertensive animals was 20.78 ± 3.36 ($p = 0.0045$).

Discussion

Many of the changes seen at 2 weeks in the vasculature of the PAAC rabbit proximal to the aortic constriction are probably part of the response of the arterial wall to a rise in pressure. The increased tangential and longitudinal stress associated with hypertension may be responsible for the increase in artery wall thickness and length — changes that are associated with an increase in the number of vascular smooth muscle cells. This is reflected in an increased capacity of the vessel wall to develop force in response to neurogenic or exogenous NE. It is of interest that

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**Figure 3.** Relationship between $^3$H-thymidine uptake and mean carotid artery pressure of rabbits 2 and 8 weeks after partial abdominal aorta constriction and their sham-operated controls. The 2-week data were obtained from previous studies by Bevan et al.

**Figure 4.** Relationship between clearance by rabbit thoracic aorta of the labelled proline and lysine and mean carotid artery pressure of rabbits 2 and 8 weeks after partial abdominal aorta constriction and their sham-operated controls. The 2-week data were obtained from previous studies by Hume and Bevan.
The relationship between carotid artery DNA content and mean carotid pressure of rabbits 2 and 8 weeks after partial abdominal aorta constriction and their sham-operated controls. The 2-week data were obtained from previous studies by Bevan et al.

The time course of cellular proliferation parallels the rise in arterial pressure.

The mechanism behind the alteration in the adrenergic innervation in this model is less clear. An increase in arterial pressure in the proximal vascular compartment would be expected to change baroreceptor activity and reflexly reduce sympathetic outflow. There is evidence that the renin-angiotensin system is not stimulated in the early phases of this model of hypertension in the rabbit. Since at 8 weeks plasma renin activity is depressed, it seems unlikely that the central nervous system contributes to the increase in parameters of peripheral adrenergic function. It is possible that the neuronal changes follow the perturbation of the blood vessel wall as a result of the arterial pressure rise.

The present study shows that at 8 weeks the cellular components of the middle-sized muscular and elastic arteries of the hypertensive vascular compartment appear to have reached a new equilibrium with respect to the raised intravascular pressure. The weight increase of thoracic, carotid, and ear arteries with rise in arterial pressure was indistinguishable from that at 2 weeks. The weights of the other vessels from the distal arterial and low pressure compartments of the circulation (with the exception of the abdominal aorta) were independent of carotid artery pressure. The increase in the abdominal aorta weight may result from increased collateral flow between the celiac and mesenteric arteries consequent upon aortic constriction. In addition, heart weight was a similar function of arterial pressure at 2 and 8 weeks.

Wall thickness was measured in vitro under conditions in which myogenic tone had been minimized. At 2 weeks, wall thickness could be closely correlated with the rise in arterial pressure. The loss of this relationship in the present series, specifically in the carotid and ear arteries, which do show a positive tissue weight increase with the rise in pressure, suggests that the vessel wall of the hypertensive animal is stiffer, i.e., retracts less after isolation compared with controls. This possibility is supported by our length measurements in vitro, in which the length of both the thoracic aorta and carotid arteries tended to be greater in hypertensive animals than in controls. This observation is consistent with our observed "reluctance" of the vessel to flatten on a glass slide after being cut longitudinally (unpublished data). Other measurements that would reflect cellular proliferation and protein synthesis within the vessel wall — such as labeled thymidine, proline, and lysine incorporation — were all independent of arterial
pressure. This reaffirms our conclusion that cellular response to pressure increase has ceased and that a new structural steady state has been established.

The DNA content of the aorta and carotid arteries could be positively correlated with the level of arterial pressure. Increase was in proportion to vessel mass. There was, however, no significant difference in the slopes or corrected means of the regression lines relating DNA content and carotid artery pressure at 2 and 8 weeks. This result shows that the cell number of the vessel wall at 2 and 8 weeks is not significantly different. As the DNA content and amino acid uptake in sham and 2-week and 8-week animals were not different, it can be concluded that the vessel wall is not in a negative balance, i.e., there is no evidence of regression of the change in response to pressure rise after 8 weeks.

A marginal increase in $^3$H-NE uptake into the adrenergic neurons of the ear artery of the 8-week hypertensive animals contrasts with the highly significant differences in the NE content, neuronal NE uptake, and contractile response to nerve stimulation seen in the earlier group. This latter measurement is considered to reflect somewhat NE release in the absence of change in NE ED$_{50}$ and diminution in NE disposition mechanisms. Alpha-receptor sensitivity changes in veins demonstrated in the earlier model could not be detected at 8 weeks. These changes in the sympathetic adrenergic systems thus appear to be short term, and may be related to the rise in arterial pressure rather than its established level. Collis and Alps$^{19,20}$ found in one-kidney renal hypertensive rats, either with or without the addition of 1% sodium chloride to the drinking water, evidence of increased NE sensitivity only in the early phase of hypertension. At 4 to 6 weeks they considered that structural changes dominated the blood vessel response to catecholamines. Data from Holloway and Bohr$^{21}$ studies of three hypertensive rat models suggest that the greatest change in NE sensitivity tends to occur early in the course of experimental hypertension.

The concept of early reversible changes in adrenergic parameters in at least some models of hypertension finds support in the literature. When NE sensitivity was measured some time after animals had reached a hypertensive state, no changes were reported. Yet alterations were observed when early stages were investigated.

In many respects the findings of this study made 8 weeks after constriction reflect and confirm observations of Wolinsky$^{27,28}$ on rats with renal hypertension. In rats remaining hypertensive for more than 1 year, Wolinsky found that early increases in heart weight and wall thickness had persisted. In our rabbit model of hypertension there is evidence that at 8 weeks a new structural equilibrium of the vessel wall has been established in response to the rise in arterial pressure. The duration of our present study was too short, however, to determine whether this change is slowly reversible. Our demonstration of a negative correlation between wall thickness in excised specimens of carotid and ear arteries and arterial pressure, a relationship not present in vessels from below the constriction, shows that such changes are not due to growth or aging. This finding is consistent with a change in the extracellular composition and thus the physical characteristics of the vessel wall.

The varying patterns of changes in vessel weight and wall thickness in this series emphasize the need for caution in generalizing from studies of one particular vessel. In the PAAC rabbit, histopathological changes varied with vessel diameter and type. In the 2-week hypertensive group during the dynamic response to arterial pressure rise there is an overall similarity in the changes in weight and wall thickness, proline and lysine uptakes, and in the time course of the $^3$H-thymidine-labeling index in the various vessels examined. During the subsequent equilibration period, however, different patterns of change appear to be emerging.

To summarize, two phases of response of the arterial wall to a rise in arterial pressure can be described. Initially, a dynamic cellular response associated with increased cell number, particularly vascular smooth muscle cells, occurs together with changes in the extracellular material. Later, an equilibrium phase is associated with a maintained increase in vascular smooth muscle cell number and changes in the extracellular components. Associated changes occur in the sympathetic and adrenergic mechanisms of the blood vessel wall. The limited data available suggest that the latter changes may reverse, despite the maintained elevation in pressure.

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