Differential structural responses of small resistance vessels to antihypertensive therapy

Toshio Sano, M.D., and Robert C. Tarazi, M.D.†

ABSTRACT Regression of left ventricular hypertrophy after control of blood pressure has been documented with some antihypertensive agents but not with others. To determine whether similar differences in regression of wall thickening also occur in resistance vessels during treatment, matched groups of spontaneously hypertensive rats (SHR) were treated for 12 weeks with either hydralazine (H) or captopril and hydrochlorothiazide (C-D) and they were compared with untreated SHR and Wistar-Kyoto rats (WKY). Perfusion pressure was then determined in the hindlimbs of pithed rats under conditions of constant blood flow (4.0 ml/min) and maximal vasodilation (hemodilution to 22% hematocrit combined with continuous nitroprusside and papaverine infusion). This perfusion pressure, which has been validated as an index of thickening (hypertrophy) of resistance vessels walls, averaged 26.8 ± 0.4(SE) mm Hg in untreated WKY (n = 12) and 37.6 ± 0.4 mm Hg in untreated SHR (n = 11) (p < .01). Treatment with H or C-D controlled blood pressure equally in SHR, but the two drugs had significantly different effects on both left ventricular hypertrophy and resistance vessels. Perfusion pressure was reduced from 37.6 ± 0.4 mm Hg to 34.0 ± 0.5 mm Hg (p < .01) with C-D but only to 36.5 ± 0.5 mm Hg with H (NS). Left ventricular weight was significantly reduced by C-D (2.02 ± 0.02 vs 2.63 ± 0.05 mg/g, p < .01) but only to 2.44 ± 0.05 mg/g by H. Close correlations were found both before and after treatment, between perfusion pressure and left ventricular weight (γ = 0.68, p < .01), but not between either of these two variables and arterial pressure. Thus, despite equal blood pressure control, wall thickness of resistance vessels regressed more with C-D than with H, suggesting that vascular hypertrophy, like left ventricular hypertrophy, is not determined by blood pressure levels alone. Moreover, thickening of resistance vessels and increased left ventricular mass, although changing in the same direction, were related to each other to a limited degree (γ² = 0.46) both during the development of hypertension and in its response to treatment.


CONSIDERABLE evidence has accumulated over the past few years demonstrating that structural changes in both the heart and peripheral vessels can develop very early in hypertension and significantly influence its course as well as its response to therapy.† More importantly, perhaps, it was suggested that these changes are not dependent solely on the prevailing level of arterial pressure, but seem to be also markedly influenced by neurohumoral factors — particularly sympathetic tone and possibly the renin-angiotensin system. Yamori et al. reported that the increased lysine incorporation in mesenteric arteries of spontaneously hypertensive rats (SHR) was markedly reduced by anatomic or pharmacologic sympathetic denervation but not by hydralazine. Bevan has convincingly demonstrated the important trophic influence of sympathetic tone in the structural responses of the rabbit’s ear vessels. Hart et al. showed that hypertrophy in cerebral arteries of SHR could be prevented by unilateral stellatectomy. Our studies both in SHR and in man have documented a marked discrepancy among otherwise equipotent antihypertensive drugs with respect to their ability to reverse left ventricular hypertrophy.

In contrast, although there have been an increasing number of studies of reversal of cardiac hypertrophy, there have been very few published reports regarding the structural response of small resistance vessels to blood pressure control. This study was therefore undertaken (1) to determine if regression of hyper-

†Deceased.
trophyc in resistance vessels could be induced in the established phase of hypertension (17-week-old SHR), (2) to determine if this regression varied with different drugs with different modes of antihypertensive action, or whether it depended on blood pressure control alone, and (3) to correlate the response to treatment of left ventricular hypertrophy with the response of small resistance vessels.

Material and methods

Twelve-week-old male SHR (n = 29) and strictly age-matched Wistar-Kyoto rats (WKY) (n = 12) from Taconic Farms (German Town, NY) were housed under exactly the same conditions, fed a standard chow (Purina chow), and received water ad librum. Blood pressure, by a tail-cuff method, and body weight were recorded regularly in all once a week. At the age of 17 weeks, the SHR were separated at random into three groups: group 1 (n = 11) was untreated; group 2 (n = 9) was given captopril (400 mg/liter) and hydrochlorothiazide (500 mg/liter) in drinking water, so that the daily intake of drugs averaged 72 mg/kg of captopril and 90 mg/kg of hydrochlorothiazide; and group 3 (n = 9) was given hydralazine in drinking water (160 mg/liter) for an average daily intake of 25 mg/kg. Treatment was continued for 12 weeks, and then all drugs were withdrawn. Papaverine (0.41 ucg/kg/min) and heparin (IU/kg) were given subcutaneously (0.41 ucg/kg/min) and heparin (IU/kg) were given subcutaneously to in drinking water, so that the daily intake of drugs averaged 72 mg/kg of captopril and 90 mg/kg of hydrochlorothiazide; and group 3 (n = 9) was given hydralazine in drinking water (160 mg/liter) for an average daily intake of 25 mg/kg. Treatment was continued for 12 weeks, and then all drugs were discontinued 24 hr before the perfusion experiment. The fourth group (n = 12) consisted of untreated WKY.

Experimental procedure for perfusion. Under ether anesthesia, the trachea of each rat was cannulated and each was pithed through the orbit with a steel rod (2.0 mm in diameter), and placed immediately on artificial respiration (0.66 ml/min) with room air, as previously described in detail. The rats were then bilaterally vagotomized, and the left carotid artery and right jugular vein of each was cannulated with PE 50 tubing for recording of systemic arterial pressure and drug infusion, respectively. The abdominal aorta was then exposed through a midline incision, and heparin (900 IU/kg) was given intravenously to prevent clotting. About 15 minutes later, the aorta was ligated distal to the renal arteries and cannulated in two places with PE 90 tubing (1) just proximal to the ligature immediately below the left renal artery and (2) distally above the aortic bifurcation. Blood from the proximal aorta was pumped into the distal aorta at a constant flow (4.0 ml/min) with a Gilson Minipuls 2 peristaltic pump. The flow rate of 4.0 ml/min was thought to be nearly physiologic flow. Perfusion pressure (value was expressed with mean perfusion pressure hereafter) was monitored by the transducer that was attached to distal cannula. The temperature of each rat was maintained at 37°C by a lamp and continuously monitored by a rectal thermometer. Pilot studies showed that perfusion pressures in the hindlimbs were maintained at the same level for at least 2-3 hr.

About 50 min after pithing, acute normovolemic hemodilution was performed by the simultaneous infusion of 6% Hextarch in 0.9% sodium chloride in total amount of 3% volume of body weight via the right jugular vein and withdrawal of blood at the same rate and volume with a Harvard pump. It usually took about 10 to 20 min for the infusion and blood was diluted to hematocrit 20% to 22%. Fifteen minutes later, nitroprusside was infused via the sidearm of the proximal aortic cannula at a constant rate of 0.0136 ml/min (100 ucg/kg/min) for 15 min; the dose was then increased to 300 ucg/kg/min at the same rate of infusion for another 15 to 20 min. During the last 5 to 10 min of this infusion, papaverine (0.41 mg/min, 0.0136 ml/min) was given, replacing a saline infusion that had been started at the same time as the nitroprusside infusion, to keep constant the total volume infused in the hindlimbs (0.0272 ml/min). Apart from the continuous recording of the hindlimb perfusion pressure at the set constant flow rate of 4.0 ml/min, perfusion pressure was also recorded as flow was changed at the end of the study from 5.0 to 3.5 and 2.0 ml/min (figure 1).

At the end of the procedure, the animals were killed by an overdose of pentobarbital. Each heart was quickly removed and cleaned; both atria and large vessels were cut away. The right ventricle was peeled from the left, and the two pieces (the right ventricle and the left ventricle with the septum attached) were washed, blotted dry, and weighed. Hindlimb weight, including skin, was measured by cutting at the level of bifurcation of the distal end of abdominal aorta.

Tests for “maximal” vasodilation. In pilot study, 20 Sprague-Dawley rats (Hilltop Laboratory, NJ) were studied in four groups. In group I (n = 6), only the standard procedure described above was performed (pithing, bilateral vagotomy, acute normovolemic hemodilution, and infusion of nitroprusside and papaverine). In the other three groups, the following was added to the standard procedure: (1) In group II (n = 5), reserpine (1 mg/kg) was injected subcutaneously 12 to 28 hr before the experiment. (2) In group III (n = 5), bilateral adenal medullectomy was performed 16 to 28 hr before the experiment. (3) In group IV (n = 4), bilateral nephrectomy was performed 6 hr before the experiment.

Statistical analyses. Values reported are mean ± SE. Analysis of variance was used for multiple group comparisons, followed by a Newman-Keuls multiple-range test. All calculations were performed on the PROPHET computer system, a resource supported in part by the National Institute of Health, Division of Research Resources. Statistical significance was defined at p < .05.

Results

Preliminary studies to test maximal vasodilation (table 1). No significant differences were present in mean arterial pressure, heart rate, or body weight among the four groups of rats used in pilot experiments to determine the degree of vasodilation. The minimal perfusion pressure (the same as perfusion pressure in maximal vasodilation) attained after pithing and infusion of nitroprusside (300 ucg/kg/min) and papaverine (0.41 mg/min) was essentially the same in all groups, irrespective of whether other pretreatment modalities were or were not used. Neither reserpine, bilateral adrenal medullectomy, nor bilateral nephrectomy resulted in perfusion pressures lower than those obtained after the standard procedure alone (table 2). Thus, the combination of pithing, acute normovolemic hemodilution, and nitroprusside and papaverine infusion apparently resulted in “maximal vasodilation,” as indicated by Folkow et al., with little if any interference from acute compensatory activation of catecholamines (adrenal or neural) or of the renin-angiotensin system.

Effect of antihypertensive therapy on the SHR groups. Treatment with either captopril-hydrochlorothiazide (group 2) or hydralazine (group 3) was begun when the rats were 17 weeks old; blood pressure fell in both groups to the same degree, reaching levels below 150 mm Hg (systolic) in 4 weeks and remaining at the
normal level for the balance (8 weeks) of the treatment period. At the time of the hemodynamic study, arterial pressure in both treated groups was significantly lower than that in untreated SHR (group 2, 127 ± 3.0 mm Hg; group 3, 133 ± 6.4 mm Hg; group 1, 212 ± 4.3 mm Hg; p < .01 for both treated groups vs group 1) (figures 2 and 3). After pithing, systolic blood pressure decreased significantly in all animals but decreased more in the treated than in the untreated SHR (group 2, 76.2 ± 3.6 mm Hg; group 3, 78.4 ± 4.7 mm Hg; group 1, 94 ± 2.8 mm Hg; p < .01 for both treated groups vs group 1). At maximal hindlimb vasodilation, the systolic pressure level recorded was not significantly different among the three SHR groups (figure 3).

There was no difference in body weight or in hindlimb weight among the SHR groups (table 3), nor was there any significant difference in heart rate after pithing (group 1, 337 ± 6.2 beats/min; group 2, 331 ± 8.0 beats/min; group 3, 341 ± 6.7 beats/min; group 4, 344 ± 7.1 beats/min; NS for all) or during maximal vasodilation (group 1, 182 ± 17.1 beats/min; group 2, 197 ± 19.5 beats/min; group 3, 214 ± 8.1 beats/min; group 4, 255 ± 14.3 beats/min; NS for all). Hematocrit was the same in all the groups before 46.7 ± 0.7%, 46.5 ± 0.4%, 46.1 ± 1.0%, and 43.1 ± 0.7%, respectively, in groups 1, 2, 3, and 4; NS for all) and after hemodilution (22.0 ± 0.3%, 22.6 ± 0.4%, 21.8 ± 0.2%, and 20.4 ± 0.6%; NS for all).

**TABLE 1**

Perfusion pressures (mm Hg) with different pretreatments at maximal vasodilation

| Group No. | Group n | Nitroprusside (100 µg/kg/min) | Nitroprusside (300 µg/kg/min) | Papaverine | Values are mean ± SE. There were no significant differences among the three treatments.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Group n</th>
<th>Nitroprusside (100 µg/kg/min)</th>
<th>Nitroprusside (300 µg/kg/min)</th>
<th>Papaverine</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>6</td>
<td>26.6 ± 0.5</td>
<td>26.4 ± 0.7</td>
<td>26.4 ± 0.6</td>
</tr>
<tr>
<td>II</td>
<td>5</td>
<td>30.9 ± 0.7</td>
<td>31.0 ± 0.7</td>
<td>30.7 ± 0.8</td>
</tr>
<tr>
<td>III</td>
<td>5</td>
<td>30.5 ± 1.7</td>
<td>30.5 ± 1.1</td>
<td>30.4 ± 1.0</td>
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<tr>
<td>IV</td>
<td>4</td>
<td>28.4 ± 1.0</td>
<td>28.5 ± 1.0</td>
<td>28.6 ± 0.9</td>
</tr>
</tbody>
</table>

Doses: 300 µg/kg/min nitroprusside and 0.41 mg/min papaverine.
TABLE 2
Perfusion pressures (mm Hg) with each maneuver

<table>
<thead>
<tr>
<th></th>
<th>After nitroprusside (100 µg/kg/min)</th>
<th>Nitroprusside (300 µg/kg/min)</th>
<th>Nitroprusside + papaverineA</th>
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<tr>
<td></td>
<td>Hemodilution</td>
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<td></td>
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<tr>
<td>Group 4</td>
<td>33.9 ± 0.7</td>
<td>26.8 ± 0.3</td>
<td>26.8 ± 0.4</td>
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<tr>
<td>Group 1</td>
<td>49.2 ± 1.4</td>
<td>37.8 ± 0.5</td>
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</tr>
<tr>
<td>Group 2</td>
<td>41.9 ± 0.7</td>
<td>34.8 ± 0.6</td>
<td>34.4 ± 0.5</td>
</tr>
<tr>
<td>Group 3</td>
<td>45.1 ± 1.2</td>
<td>36.4 ± 0.4</td>
<td>36.7 ± 0.5</td>
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</table>

Statistical significance

<table>
<thead>
<tr>
<th></th>
<th>1 vs 2</th>
<th>1 vs 3</th>
<th>2 vs 3</th>
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</tr>
<tr>
<td>p</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>p</td>
<td>&lt;.01</td>
<td>NS</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Values are mean ± SE.
A Doses: 300 µg/kg/min nitroprusside and 0.41 mg/min papaverine.

3 at all flow rates. The minimal perfusion pressure in that latter group was altered to a questionable degree by therapy: it was not significantly different from that in group 1 except at a flow rate of 2.0 ml/min.

The hindlimb minimal perfusion pressure in all SHR, both treated and untreated, seemed to remain higher than that in group 4 at all flow rates (table 4). However, comparison between SHR and WKY was difficult, because the body weights of the WKY were much greater than those of the SHR (table 3) and a method of accurate correction for this difference to allow comparison of minimal perfusion pressures in SHR and WKY was not clear.

Effect of treatment on left ventricular weight (table 3). Both modalities of antihypertensive treatment reduced left ventricular weight, albeit by different degrees. In group 1, left ventricular weight averaged 2.63 ± 0.05 mg/g body weight; in group 2 it decreased to 2.02 ± 0.02 mg/g (p < .01), but in group 3 it decreased significantly less (to 2.44 ± 0.05 mg/g), even though blood pressure control was equal in the two treated groups. Statistical comparison resulted in a p value of

![Figure 2](http://circ.ahajournals.org/)

**FIGURE 2.** Course of systolic pressure (BP), as measured by tail cuff, over 12 weeks in WKY and SHR. SHR-no Rx = group 1; SHR-C + D = group 2; SHR-H = group 3; WKY-no Rx = group 4. Curve is accompanied by SE. *Significant difference between SHR-C + D and SHR-H (p < .01).
FIGURE 3. Systolic pressure in SHR and WKY before and after operation. *Measured by tail cuff just before operation in the last week of 12 week therapy. **Measured intra-arterially in left carotid artery after operation.

for both group 3 vs group 1 and group 3 vs group 2 values. In neither case, however, was left ventricular weight "normalized," since it remained significantly higher than that in group 4 (1.81 ± 0.04 mg/g).

A significant correlation was found between minimal perfusion pressure and left ventricular weight among SHR whether calculated for all (γ = 0.68, p < .01) or only for the treated groups (γ = 0.68, p < .01) (figure 5).

Discussion

Minimal perfusion pressure as an index of the ratio of wall thickness to internal radius in small resistance vessels. Folkow et al.16 have demonstrated, in a series of careful studies, a close correlation between minimal perfusion pressure and the ratio of wall thickness to internal radius in small resistance vessels. This approach provided a significant advance for investigators of structural changes in these vessels at various phases of hypertension and in response to treatment, resolving some of the difficulties with direct determination of small vessel morphology and exact comparison between individual specimens or between experimental groups.13 17 It also provided the only ethically accept-
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TABLE 4
Perfusion pressures (mm Hg) at different flow rates in SHR and WKY at maximal vasodilation

<table>
<thead>
<tr>
<th>Flow rate (ml/min)</th>
<th>2.0</th>
<th>3.5</th>
<th>4.0</th>
<th>5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 4</td>
<td>16.1±0.3</td>
<td>23.4±0.3</td>
<td>26.8±0.4</td>
<td>29.6±0.4</td>
</tr>
<tr>
<td>Group 1</td>
<td>23.6±0.5</td>
<td>33.4±0.6</td>
<td>37.6±0.4</td>
<td>41.8±0.7</td>
</tr>
<tr>
<td>Group 2</td>
<td>20.7±0.3</td>
<td>30.3±0.5</td>
<td>34.0±0.5</td>
<td>38.1±0.6</td>
</tr>
<tr>
<td>Group 3</td>
<td>22.2±0.6</td>
<td>32.2±0.4</td>
<td>36.5±0.5</td>
<td>40.3±0.6</td>
</tr>
</tbody>
</table>

Statistical significance

1 vs 2 p<.01  p<.01  p<.01  p<.01
1 vs 3 p<.05  NS       NS       NS       NS
2 vs 3 p<.05  p<.05  p<.01  p<.05

Values are mean ± SE.

the results obtained from the stepwise addition of these maneuvers in the data analysis (table 2). After pithing alone, systolic pressure in untreated SHR was higher than in WKY (figure 3), an observation in agreement with the results reported by Okamoto et al. The blood pressure of the adult SHR in their study remained higher than control after disconnection of its control from the central nervous system by encéphale isolé and pithing. However, blood pressure fell to the same level in SHR and WKY when hemodilution, nitroprusside, and papaverine were added to the pithing protocol. It appeared that, without neurohumoral influence, at maximal vasodilation resistance vessels could not maintain the high level of blood pressure.

Acute normovolemic hemodilution was used for vasodilation and to minimize the influence of possible differences in viscosity on perfusion pressure. We chose to reduce hematocrit to about 22%.

Haynes showed that apparent viscosity of blood in a tube 57 μm in diameter decreased with hemodilution, but was almost constant under a hematocrit of 30%. Levy and Share have confirmed Haynes’ findings in dog. Furthermore, it has been shown that no change in oxyhemoglobin affinity occurs during acute

FIGURE 4. Perfusion pressure during maximal vasodilation (MPP) at different flow rates (2.0, 3.5, 4.0, 5.0 ml/min). The difference between SHR-no Rx (group 1) and SHR-C + D (group 2) was significant at all levels of flow, whereas the difference between SHR-no Rx and SHR-H (group 3) was not significant except at a flow rate of 2.0 ml/min (see also table 4).

FIGURE 5. Relationship between left ventricular weight normalized for body weight (LV/BW) and perfusion pressure at a flow rate of 4.0 ml/min. Correlation coefficient is $r = .68$; index of determination is $r^2 = .46$. 
normovolemic hemodilution to a 20% hematocrit. To replace the blood withdrawn, we have used a 6% hetastarch solution to maintain colloid osmotic pressure and avoid tissue edema. Susic et al. showed that reducing the hematocrit could lower the elevated blood pressure of SHR.

In summary, the perfusion pressures produced by a combination of pithing, acute normovolemic hemodilution, and high doses of nonspecific vasodilators appear to represent the “minimal” pressure level achievable, and thus to be related to structural alterations in the small resistance vessels, as shown by Folkow et al. Under these conditions of constant flow and maximal vasodilation, it is possible to determine with precision the role played by even small changes in vascular lumen since resistance is inversely proportional to the fourth power of the vessels’ internal radius. Perfusion pressure is influenced by resistance vessels, larger arteries that feed the resistance vessels, and other conditions. Characteristics of the resistance vessels are important factors in the hypertension of SHR. Small structural changes in resistance vessels are well reflected in perfusion pressure, even at maximal vasodilation, as has been shown repeatedly by Folkow and his colleagues. By examination of these changes, the vascular bed of genetically hypertensive rats has been found to display increased resistance, a result in agreement with the morphologic studies of Mulvany et al., who reported narrowed lumen, thickened media, and an increased smooth muscle cell layer in SHR as compared with WKY. Furthermore, Yamori et al. reported that protein synthesis in cell cultures of vascular smooth muscle cells from SHR was more increased than that in cells from WKY, independent of blood pressure.

Blood pressure control and cardiovascular hypertrophy. The main results of our study indicate that thickening of small resistance vessels (as inferred from changes in minimal perfusion pressure) can regress with antihypertensive therapy but that this regression was not dependent on blood pressure control alone. Despite equal blood pressure levels during treatment, minimal perfusion pressure was reduced significantly more in captopril-hydrochlorothiazide–treated than in hydralazine-treated SHR (table 4; figure 4). The same results were observed with regard to changes in left ventricular mass; cardiac hypertrophy regressed significantly more with the former therapy than with the latter (table 3). These observations of a reduction in left ventricular mass and a more marked vascular effect are in agreement with previous reports. Sen and his colleagues have previously reported a greater effectiveness of captopril in reversing left ventricular hypertrophy in SHR and observed only borderline changes with hydralazine. In a “preventive” study in 8-week-old SHR, Freslon et al. observed a 30% decrease in wall-to-lumen ratio in the mesenteric artery after 14 weeks of captopril therapy, but only a 15% decrease with hydralazine. Limas et al. reported that 6 weeks of treatment with captopril in 21-week-old SHR significantly reduced the wall thickness in small intrarenal vessels and that hydralazine was not as effective as captopril in this respect.

In contrast with these results, however, Lundin et al. showed that drugs with different modes of hypotensive action (adrenergic β-blockers, calcium-entry blockers, and α-methyldopa) led to regression of structural cardiovascular changes in SHR in direct proportion to their effects on arterial pressure. Warshaw et al. reported a linear relationship between blood pressure and smooth muscle cell content in mesenteric arteries of treated and untreated SHR. Some of the discrepancies among various reports are probably due to the methods used, the size of arteries investigated, and the different durations of therapy. Moreover, it must be pointed out that even in the studies showing a relationship between blood pressure control and structural changes, the correlation was not close. It would appear that there are on balance some real differences among hypotensive agents with respect to their potential for reversal of cardiovascular hypertrophy. This was particularly clear in our results and those of others who compared captopril and hydralazine. The difference between the treated groups may be due to the fact that hydralazine triggers a marked rise in sympathetic excitation but captopril-hydrochlorothiazide does not. The level of sympathetic outflow can change the thickness of the media in resistance vessels.

The results in our study differ from those of Lundin et al. This may be due to the different influences of the drugs used on the sympathetic nervous system, which could be caused by differences in the degree of reflex sympathetic stimulation or in levels of angiotensin. However, the data of the present study do not allow a firm conclusion as to the mechanisms involved, nor is it possible to determine the relative roles played by the diuretic agent and the converting-enzyme inhibitor in the combination that led to regression of cardiovascular hypertrophy. Although hydrochlorothiazide has not been observed to lead to regression of cardiac hypertrophy in previous studies in SHR or in patients, direct comparative studies are needed to answer this question precisely. The important point remains, however, that of two antihypertensive regi-
Correlation of cardiac and vascular effects of antihypertensive treatment. Few if any reported studies have specifically addressed the correlation between the effects of antihypertensive therapy on the heart and small resistance vessels in the same experimental animals. We have found a close correlation ($\gamma = 0.68$) between minimal perfusion pressure and left ventricular weight in treated SHR, and the same correlation held when data from untreated SHR were included in the analysis (figure 5). Neither index (left ventricular weight or minimal perfusion pressure) significantly correlated with arterial pressure levels. Although these results suggest some parallelism in the structural response to treatment between the heart and small vessels, the index of determination ($\gamma^2 = 0.46$) was not very close, pointing to the possibility of discrepancies in the hypertrophic responses of the two tissues to hypertension. More studies with different types of agents are needed to investigate this possibility. In that context, differences have also been reported between the responses of the heart and large vessel to hypertension and blood pressure control. As more studies become available, a clearer picture will emerge regarding the degree of variability in structural responses to hypertension of different parts of the cardiovascular system.

The implications of these experimental studies for antihypertensive therapy are of great importance. To the extent that cardiovascular hypertrophy contributes to the evolution and complications of hypertension, its reversal by appropriate treatment becomes an important independent goal along with blood pressure control. This is particularly evident for hypertrophy of resistance vessels, which can help maintain increased vascular resistance and amplify the vasoconstrictor response even to normal stimuli. Return toward normal of the wall-to-lumen ratio in these vessels will make control of arterial pressure easier and possibly result in longer periods of remission.

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