Perindopril Treatment Affects Both Preglomerular Renal Vascular Lumen Dimensions and In Vivo Responsiveness to Vasoconstrictors in Spontaneously Hypertensive Rats

Göran Bergström, Inger Johansson, Kathleen M. Stevenson, Michelle M. Kett, Warwick P. Anderson

Abstract—We have previously shown that chronic treatment with angiotensin-converting enzyme inhibition (ACEI) did not reverse hypertrophy of the renal arterial wall in spontaneously hypertensive rats (SHR). In this study we determined the effects of perindopril on the functional properties of the renal vasculature in vivo and on its resistance to flow at maximal dilatation in vitro, a measure of vessel lumen diameter. Two groups of SHR were studied: untreated or treated with perindopril (3 mg/kg per day) in their drinking water from 4 weeks of age. At 10 weeks, (1) vessel lumen characteristics were assessed using a maximally dilated in vitro isolated kidney perfusion and (2) the renal vasoconstrictor responses to bolus doses of vasoactive agents (angiotensin II and phenylephrine) administered into the renal artery were measured in vivo (anesthetized rats). Mean arterial pressure was significantly lower in conscious SHR treated with perindopril (132±2 versus 97±2 mm Hg, P<.001). In vitro, the pressure-flow relationship and the pressure–glomerular filtration rate relationship were both shifted significantly to the left (P<.001). The perindopril-treated kidneys began filtering at a significantly lower threshold perfusion pressure than nontreated controls (P<.001). In vivo, renal vasoconstrictor responses to increasing doses of both vasoconstrictor agents were significantly less marked in the perindopril-treated SHR than in untreated SHR (P<.05). Thus, chronic ACEI increased average renal vessel lumen diameter in SHR, predominantly in preglomerular vessels, and reduced renal vasoconstrictor responsiveness in vivo, findings compatible with remodeling of the preglomerular vasculature around a greater lumen. (Hypertension. 1998;31:1007-1013.)

Key Words: angiotensin-converting enzyme inhibitors ◼ kidney ◼ perfusion ◼ rats, inbred SHR ◼ vascular resistance

The walls of the pregglomerular vessels of the SHR are thicker than those of the normotensive Wistar-Kyoto rat1–3 and their vascular lumen is narrower.3–8 We have shown that treatment with an ACEI from weaning did not appear to reduce wall thickening of the interlobular and arcuate arteries in SHR vessels despite normalization of blood pressure.5 This is in contrast to the known effects of chronic ACEI treatment in other vascular beds.9–11

Our previous study of the renal vessel response to ACEI was stereological, with kidneys fixed at physiological pressures.2 While this study provided accurate estimates of wall dimensions, it did not provide reliable lumen dimensions. This was due to the fact that the prevailing physiological conditions will have determined smooth muscle tone, and therefore vessel radius, and because of possible fixation artifacts. Thus, it was not possible in this morphometric study to document whether the wall hypertrophy had resulted in lumen encroachment or to determine how the wall dimensions affected renal vascular properties in vivo.

The aim of the present study was to determine the effects of chronic ACEI treatment on the renal vessel lumen characteristics and to assess in vivo renal vascular responsiveness to vasoactive agents, as an indicator of the functional significance of the wall and lumen dimensions in vivo. The lumen characteristics of the renal vasculature were hemodynamically assessed using the in vitro, maximally dilated, whole kidney perfusion technique of Göthberg et al.8,12 The effects on resistance vessel behavior in vivo, as an index of the “vascular amplifier” properties of the vessels as developed by Korner and Angus,13 were assessed by measuring RBF responses to doses of vasoactive agents administered directly into the renal artery.

Methods

Male SHR (n=35), bred at the Baker Medical Research Institute, Prahran, Victoria, Australia, were housed 2 to 4 per cage in a room maintained at a constant temperature (23°C to 25°C) with a 12-hour light/dark cycle. Standard rat chow and water were supplied ad libitum. The experiments were approved in advance by the Alfred Hospital/Baker Institute Animal Experimentation Committee and Monash University Standing Committee on Ethics in Animal Experimentation as being in accord with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. At 4 weeks of age, all rats were randomly assigned to receive either perindopril 3 mg/kg per day (a gift from Servier, Melbourne, Victoria, Australia) or tap water. The dose was adjusted three times weekly after measurement of water intake and body weight. Treatment continued until the day of the experiment (10 weeks of age). To minimize confounding effects of different levels of Ang II concen-
Measured osmolarity in the perfusate was 300 mOsm/L. The P O 2 of 903 mm Hg when bubbled with 95% O 2 and 5% CO 2.

This part of the experiment.

In Vitro Studies of Renal Vascular Structure

Initially on the experimental day, blood pressure was measured in awake rats through the tail artery. The tail artery was cannulated (PE-50) with rats under short-acting anesthesia (methohexitone sodium, Eli Lilly, 75 mg/kg IP), and then awake MAP was recorded 60 minutes after cannulation for a period of 10 minutes. The rats were then anesthetized with pentobarbitone sodium (60 mg/kg IP; Nembutal, Boehringer Ingelheim) and placed on a warm operating table. Once a surgical level of anesthesia was established, tracheotomy and cannulation of the left jugular vein (PE-50) were performed, and a continuous infusion of pentobarbitone (5 mg/h) and 2% BSA (Sigma Chemical Co) was begun (6 mL/h during surgery and then 1.8 mL/h). The intestines were removed through a midline incision, and the abdominal aorta was isolated 1 cm proximally and distally to the left renal artery. The left ureter was cannulated (PE-10, 6 cm) for collection of urine, and the mesenteric artery was cannulated (PE-50) for measurement of aortic pressure close to the left renal artery. This pressure was taken as the kidney arterial inflow pressure. All visible branches from the isolated aorta were ligated except for the left renal artery and mesenteric artery. After heparinization (3000 U/kg IV), a PE-90 catheter connected to the perfusion setup was inserted retrogradely into the distal aorta toward the left kidney, and the perfusion to the left kidney was started at room temperature (20°C to 23°C). Immediately afterward, the aorta was tied off just above the mesenteric artery, the renal vein was cut, and the animal was killed by an overdose of pentobarbitone. The renal capsule was removed to minimize increments in renal tissue pressure. Perindopril was added to the perfusate to rule out spontaneous hypertensive rats.

The perfusate consisted of a modified Tyrode solution containing Na+ 148, K+ 4.3, Cl– 133, Ca2+ 2.5, Mg2+ 0.8, HCO3– 25, H2PO4– 0.5, t-glucose 5.6 mmol/L, dextan 70 20 g/L, with a pH of 7.4, and PO2 of 903 mm Hg when bubbled with 95% O2 and 5% CO2. Measured osmolarity in the perfusate was 300 mOsm/L. The perfusate included 0.04 μCi/mL [3H]inulin (NEN Research Products) for measurement of GFR, 0.9 mmol/L sodium nitroprusside (Sigma), 100 mmol/L perindopril, and 10 mg/L furosemide (Alpha-pharm Pty Ltd). The nitroprusside and the low perfusion temperature (20°C to 23°C) assured that the kidney vasculature was maximally vasodilated. This was further tested in additional experiments (n=4) in which an infusion of acetycholine (0.07 mg/min) did not further dilate the vasculature. Furosemide was added to inhibit tubuloglomerular feedback, and it also facilitated collection of urine at low perfusion pressures. Perindopril was added to the perfusate to rule out confounding effects of differences in the levels of tissue perindopril and thereby Ang II. Throughout the study, the perfusate was kept at room temperature (20°C to 23°C) and protected from light.

Thirty minutes after the perfusion was started, collections of urine and measurements of perfusion pressure and interstitial pressure were repeated during seven to eight stepwise increments of perfusion flow from 2.6 mL/min to ~25 mL/min. 5,12 Urinary volume was measured gravimetrically. After the final measurement, the perfusate was changed to an identical perfusate except that it did not include nitroprusside. The perfusion was continued at 2.6 mL/min, and 20 minutes later, phenylephrine (100 μmol/L; Sigma), [Arg9]vasopressin (1.25 μmol/L; Australian Laboratory Services), and Ang II (1.0 μmol/L; Auspep Pty Ltd) dissolved in Tyrode solution were added to the perfusate for 5 minutes to assess the maximal renal vasoconstrictor response. In pilot experiments, bolus injections of 25 mmol/L BaCl2 at the end of this infusion did not constrict the vessels further, indicating that the vessels were maximally constricted. After the experiment, the perfused left kidneys were desiccated in a heating chamber at 70°C for 48 hours to determine dry kidney weight.

In Vivo Studies of Renal Vascular Responsiveness

The rats were anesthetized and initially prepared as above. The right femoral artery was catheterized (PE-50) for arterial blood pressure measurement. A midline abdominal incision was performed, and the urinary bladder was cannulated (PE-160) to drain urine. The left renal artery and the aorta were isolated, and the renal artery and vein were stripped and painted with 70% alcohol. A tapered PE-10 catheter was inserted into the left femoral artery and passed up through the aorta. The catheter tip was gently introduced into the left renal artery 1 to 2 mm to allow for administration of vasoactive agents directly into the renal vascular bed. Heparinized saline was infused through the renal artery catheter at 5 μL/min to maintain patency of the catheter. A 1-mm Transonic mean transit-time flow probe (Transonic Systems Inc) was placed around the renal artery. After completion of surgery, the rats were allowed 30 minutes to stabilize, and perindopril (2 mg/kg IV) was administered to both groups. Body temperature was maintained at 38°C by the heating table and a heating lamp.

Ang II (2, 4, 8, and 16 ng) and phenylephrine (0.5, 1, 2, and 4 μg; Sigma) were administered into the renal artery in increasing bolus volumes of 5, 10, 20, and 40 μL, respectively, with 5 minutes between each dose. Administration of vehicle in these volumes had no effect on RBF or blood pressure. After the final dose of each vasoactive agent, at least 15 minutes was allowed before the next agent was administered.

Data Collection, Calculations, and Statistics

In the in vivo experiments, as well as perfusion experiments, pressure was measured by a Statham P23DC strain-gauge pressure transducer. The signals were amplified and recorded on a Grass model 7 polygraph and collected on an Olivetti M 24 computer equipped with an analog-to-digital converter and data acquisition software (Baker Medical Research Institute, Prahran, Australia).

In the isolated kidney, perfusion flow, arterial distending pressure, and GFR were used to estimate the relationship between flow and pressure and the relationship between pressure and GFR at maximal vasodilatation. Arterial distending pressure in the isolated kidney was calculated as arterial inflow pressure minus renal tissue pressure (ie, the needle pressure). Because there was a small difference in the renal tissue pressures between the two groups (see “Results”), we also analyzed the relationship between arterial inflow pressure and flow and arterial inflow pressure and GFR. GFR was calculated as [3H]inulin clearance. Renal measurements in vitro were all expressed as kidney dry weight.

In the in vivo experiments, renovascular resistance (RVR) and conductance were calculated from MAP and RBF and expressed per kidney wet weight. A nominal internal radius was also calculated using Poiseuille’s relationship, r = √(1/RVR).13 This provides a notional estimate of the effective overall radius of the vessels offering resistance to flow. At the end of the experiment, the left kidney was weighed, and the doses of vasoactive agent received by individual rats were expressed per gram of wet kidney weight. Individual rat data from the in vivo experiments were fitted to cubic spline graphs that were used to normalize the doses received by the different kidneys (Sigmaplot, version 2.0, Jandel Scientific). At the end of all
Hemodynamics and Organ Weights in Perindopril-Treated SHR

<table>
<thead>
<tr>
<th></th>
<th>Untreated (n=9)</th>
<th>Perindopril-Treated (n=10)</th>
<th>P</th>
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<tbody>
<tr>
<td>MAP, mm Hg*</td>
<td>132±2</td>
<td>97±2</td>
<td>.000</td>
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<tr>
<td>Left ventricle, g/100 g BW*</td>
<td>0.244±0.004</td>
<td>0.185±0.004</td>
<td>.000</td>
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<tr>
<td>Right ventricle, g/100 g BW*</td>
<td>0.072±0.003</td>
<td>0.069±0.003</td>
<td>.493</td>
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<tr>
<td>Kidney wet weight, g</td>
<td>1.537±0.051</td>
<td>1.388±0.036</td>
<td>.033</td>
</tr>
<tr>
<td>Kidney dry weight, g</td>
<td>0.219±0.007</td>
<td>0.215±0.005</td>
<td>.629</td>
</tr>
<tr>
<td>BW, g</td>
<td>257±4</td>
<td>243±5</td>
<td>.048</td>
</tr>
<tr>
<td>Max pressor response, mm Hg</td>
<td>226±15</td>
<td>170±5</td>
<td>.004</td>
</tr>
<tr>
<td>Max RVR, mm Hg · mL⁻¹ · g dry kidney wt⁻¹ · min⁻¹</td>
<td>16.30±1.20</td>
<td>12.09±0.35</td>
<td>.004</td>
</tr>
</tbody>
</table>

BW indicates body weight; RVR, renovascular resistance.

*Body weight (n=17), MAP (n=11), and heart weight (n=17) are pooled from both experiments.

Results

Body, Heart, and Kidney Weights and Awake MAP

Body, heart, and kidney weights for rats used in the in vitro and in vivo experiments are shown in the Table. The perindopril-treated group had a significantly lower awake MAP than their controls (97±2 versus 132±2 mm Hg, P<.001). Left ventricular heart weights were significantly greater in the nontreated group (P<.001) compared with the control group (Table). There was no significant difference in heart rate between the groups (data not given).

In Vitro Hemodynamic Assessment of Renal Vessel Structure: Perfusion of Isolated Kidneys (n=8 Pairs)

The relationships between perfusion flow and distending arterial pressure in the isolated perfused kidneys are shown in Fig 1. Regression analysis showed a significant linear relationship within each individual experiment, with Pearson correlation coefficients (R²) ranging from .992 to 1.000. The relationship between arterial distending pressure (inflow pressure minus tissue pressure) and flow was significantly shifted to the left in the perindopril-treated kidneys (ie, significant change in intercept, P<.001) with a significant change in slope (P<.001). When the relationship between arterial inflow pressure and flow was analyzed, there was still a significant difference in both slope (P<.001) and intercept (P<.001) of the line.

Arterial distending pressure and GFR (Fig 2) also showed a significant linear relationship within each individual experiment, with Pearson correlation coefficients ranging from .776 to 1.000. The relationship between arterial distending pressure and GFR was also significantly different between the two groups, with the relationship in the perindopril-treated SHR shifted significantly to the left (P<.001) and with a change in the slope of the relationship (P<.001). The extrapolated intersection with the abscissa (starting point for filtration) was 52±3.4 mm Hg for the control SHR and 18±3.2 mm Hg for the perindopril-treated SHR. When the relationship between arterial inflow pressure and GFR was analyzed, there was a significant difference in both slope (P<.001) and intercept (P<.001) of the relationship.

In both groups, renal tissue pressure increased concomitant with the increase in arterial distending pressure and was 13±1 mm Hg at an arterial inflow pressure of 80 mm Hg in the control SHR and 28±3 at 140 mm Hg. Renal tissue
pressure in the perindopril-treated SHR was approximately 5 mm Hg higher than that of the control SHR across the full range of perfusion pressures \((P<.001)\).

The arterial distending pressure and total renal vascular resistance response to supramaximal doses of vasoconstrictors were lower in the perindopril-treated compared with control kidneys (Table).

**In Vivo Studies of Renal Vascular Responsiveness**

After anesthesia of the rat and completion of surgery, MAP was \(128 \pm 2\) mm Hg in the untreated \((n=9)\) and \(97 \pm 3\) mm Hg in perindopril-treated SHR \((n=10, P<.001)\).

Left (denervated) RBF was not significantly different between untreated \((7.59 \pm 0.83 \text{ mL} \cdot \text{min}^{-1} \cdot \text{g kidney wt}^{-1})\) and treated SHR \((7.00 \pm 0.54 \text{ mL} \cdot \text{min}^{-1} \cdot \text{g kidney wt}^{-1}, P=.517)\).

Renal vascular resistance was \(18.62 \pm 2.16\) and \(14.25 \pm 0.83 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{min}^{-1} \cdot \text{g kidney wt}^{-1}\), respectively \((P=.066)\).

Increasing doses of both vasoconstrictors produced dose-related falls in RBF (Figs 3b and 4b). At the time of peak renal response to the agent, MAP was minimally affected at the low doses \((1 \text{ to } 3 \text{ mm Hg})\) but rose by \(\sim 10\) to \(15 \text{ mm Hg}\) at the highest dose (Figs 3b and 4b).

RBF, vascular resistance, and vascular conductance responses to the vasoactive agents are plotted in Figs 3a and 4a. The effect of Ang II on RBF was significantly greater in the untreated SHR compared with treated, as exemplified by the steeper slope of the untreated SHR curve \((P<.05)\). This difference was also evident when analyzing renal vascular resistance. Renal vascular resistance changed significantly more in response to Ang II in the untreated compared with perindopril-treated SHR \((P<.01)\). The changes in renal vascular conductance in the untreated SHR in response to Ang II paralleled the changes in perindopril-treated SHR.

The RBF responses to phenylephrine were similar to those seen with Ang II (Fig 4). Phenylephrine resulted in dose-dependent decreases in RBF that returned to control values before administration of the next dose. No major effect was seen on blood pressure. For statistics see “Methods.” RVR indicates renovascular resistance.
curve of the perindopril-treated SHR was shifted significantly to the right compared with control. At the highest doses of phenylephrine, renal vascular conductance more closely approached zero in the untreated SHR (Fig 4a).

Calculated “nominal” radius of the renal vasculature (Poiseuille’s formula, see “Methods”) and the response of the radius to the two agents are shown in Figs 3a and 4a. The results indicated a smaller effective “radius” of resistance vessels in the untreated SHR renal vascular bed across the full range of vasoconstriction (Ang II, \( P < .05 \); phenylephrine, \( P < .01 \)).

**Discussion**

Hypertension is associated with structural changes in vessel design.\textsuperscript{16,17} There is, however, still debate about the exact morphological nature of this redesign, about which vascular beds and which parts of the vascular tree are affected, and importantly, about the significance of these changes for in vivo vascular responsiveness and blood pressure control.\textsuperscript{18,19} While differences in renal vascular responsiveness can be demonstrated in vitro, their significance in vivo will be affected by homeostatic mechanisms and/or pathological changes that may either potentiate or ameliorate the underlying structurally based vascular responsiveness.\textsuperscript{19} This especially holds true in the kidney, where glomerular filtration, tubular handling of the ultrafiltrate, and intrarenal control mechanisms (eg, tubuloglomerular feedback) may confound and render both the in vitro and in vivo results difficult to interpret.\textsuperscript{3} This study was designed as an integrative approach to investigate the effects of ACEI treatment on renal vascular lumen dimensions in SHR and in what form these changes translate into differences in the in vivo renal vascular responsiveness to vasoconstrictor agents.

To investigate the effects of ACEI treatment on renal vascular resistance at maximal dilatation, as an index of renal vascular lumen dimensions, we used a modified version of the functional in vitro perfusion technique developed by Göthberg and colleagues.\textsuperscript{5} With this hemodynamic technique, it is possible to detect changes in renal vascular lumen dimensions with great accuracy because resistance changes with the fourth power of the radius. Furthermore, the technique can indicate whether these changes are confined to the pre- or postglomerular circulation. The results from Göthberg’s hemodynamic studies\textsuperscript{4,5,8} are in good agreement with other techniques applied to estimate lumen dimensions of the renal vascular bed.\textsuperscript{6,7,20}

In the present study, the pressure-flow relationship in the perindopril-treated kidneys was clearly shifted to the left, representing a decrease in the total renovascular resistance at maximal dilatation across a wide range of perfusion pressures. We conclude from this finding that perindopril increased the average lumen of the resistance vasculature, which was maximally dilated during the experiment.

The interpretation of the pressure-GFR relationship is more complex. In the maximally vasodilated isolated pump–perfused kidney, neurohormonal and active autoregulatory control systems are assumed to be inoperative, and therefore glomerular filtration is mainly determined by the following three factors: (1) intraglomerular hydrostatic pressure, which is influenced by the perfusion pressure and the pre- to postglomerular resistance ratio, (2) the whole kidney ultrafiltration coefficient, ie, the total glomerular surface area multiplied by mean hydraulic conductance, and (3) the proximal intratubular pressure. These three factors affect the slope and the position of the pressure-GFR relationship in the maximally dilated kidney in different ways. The slope of the relationship will reflect both the filtration capacity of the kidney and the pre- to postglomerular resistance ratio.\textsuperscript{4,5} On the other hand, the position of the relationship along the abscissa and its intercept with the x axis will be determined by the pre- to postglomerular resistance ratio.\textsuperscript{4,5} Resultant changes in intraglomerular pressure minus tubular pressure will determine GFR.

The pressure-GFR relationship in the perindopril-treated SHR was shifted to the left compared with the untreated group, with the x axis intercept at about 20 mm Hg compared
with about 50 mm Hg for the untreated SHR (Fig 2). This pattern is the expected change in the pressure-GFR relationship if the pre- to postglomerular resistance ratio is lowered.\(^5,5\)

We cannot, however, rule out the possibility that there is a simultaneous minor change in the whole kidney ultrafiltration coefficient. However, we have found previously that chronic treatment with the selective angiotensin type 1 receptor antagonist TCV-116 failed to affect either glomerular volume or total glomerular capillary surface area in SHR at this age.\(^5\)

We therefore conclude that the leftward shift of the pressure-GFR relationship is most readily interpreted as a decrease in the pre- to postglomerular resistance ratio in the maximally dilated kidney of rats treated chronically with ACEI. The conclusion from the in vitro part of the experiment is that perindopril treatment increases the average renal vascular lumen diameter, and it does so predominantly in the preglobular circulation. Our techniques do not allow us to conclude whether this occurs in the afferent arteriole, larger upstream vessels, or both.

There are technical difficulties in studying hemodynamic behavior in isolated perfused kidneys, which are not encountered in other vascular beds. Most important is the fact that the kidneys under these circumstances exhibit a high degree of passive autoregulation, believed to be caused mainly by an increase in tubular pressure generated by the high glomerular filtration and reduced tubular reabsorption.\(^22,23\) When the kidneys are perfused at increasing pressures, the glomerular ultrafiltrate will distend the tubules. The intratubular pressure will be transmitted to the interstitium and build up a significant hydrostatic pressure in the kidney (see “Results”). Consequently, the increased tissue pressure will decrease the transmural pressure of the kidney vasculature and act to increase renal resistance by reducing the bore of vessel lumens, especially on the low-pressure venous side of the circulation. Göthberg and colleagues\(^5\) showed in a set of ingenious experiments with kerosene-perfused kidneys that this passive autoregulation in the perfused kidney can lead to erroneous conclusions regarding renovascular resistance if the increase in tissue pressure is ignored. In this study, we attempted to minimize the buildup of renal tissue pressure by removing the capsule of the kidney,\(^5\) and we measured tissue pressure in all experiments with a needle inserted into the kidney at a midcortical depth.\(^5,5\) This pressure was subtracted from the arterial inflow pressure to give a more accurate estimate of the “arterial distending” pressure.\(^5\)

There was a small difference in the renal tissue pressure between the two groups with an \(\approx 5\) mm Hg greater pressure in ACEI-treated SHR across all perfusion pressures (\(P<.001\)). Because this difference may affect the position of the pressure-flow and pressure-GFR relationship, and thus the conclusions, we also performed the statistical analysis of these data using arterial inflow pressure instead of arterial distending pressure (see “Methods”). However, this made little difference to the analysis (see “Results”), and we therefore concluded that the observed minor difference in tissue pressure was of no major importance.

The maximum contractile response showed a 34% higher maximum renovascular resistance achieved in the nontreated SHR (Table). This suggests that perindopril markedly lowers the average maximal contractile strength of the renal vascular wall in relation to its lumen size. If we assume that the contractile strength of the vessel wall is unchanged, we can conclude that there is a decrease in the wall to lumen ratio in the renal vessels. This conclusion is supported by our previous finding that the wall size is not changed after ACEI treatment.\(^5\) However, it is possible that ACEI may have had effects on the contractile properties of the vessel wall, causing intracellular changes or changes in the mechanical coupling of the elements of the vascular wall.

We have shown previously that ACEI treatment during the same time interval as in the present study did not affect wall dimensions of the interlobular and arcuate arteries in SHR.\(^2\) The in vitro finding in the present study shows that chronic ACEI treatment resulted in an increase in the average lumen of the maximally dilated renal vessels and that this seems to occur predominantly in the preglobular circulation. This is compatible with another recent study showing that the afferent arteriolar diameter is greater in ACEI-treated SHR compared with nontreated controls.\(^25\) Analyzed together with our previous findings, these results suggest that ACEI remodels the same amount of vascular wall around a greater lumen. Expressed in terms of remodeling, the observed vascular changes can be described as outward, eutrophic remodeling.\(^26\)

It is also possible that chronic perindopril affects the mechanical properties of the vascular wall and thereby affects the vascular stiffness and compliance (eg, through changes in connective tissue). This demands further study.

How is in vivo hemodynamic behavior of the renal resistance vessels affected by these ACEI-induced changes in vascular structure? We addressed this question by performing dose-response curves to two vasoconstrictor agents, injecting the agents directly into the renal artery in vivo. Ang II and phenylephrine were chosen because they have different receptor and second messenger pathways. Thus, similar findings with these two dissimilar agents indicate that the results are due to vessel geometry rather than changes in receptor density, second messengers, or endothelial function, for example. Furthermore, both agents have rapid onset effects on RBF and are rapidly metabolized, thereby minimizing effects due to systemic spill-over and accumulation of the agent.

The contractility of the smooth muscles in the vasculature, and hence its responsiveness to vasoconstrictors, is strongly dependent on vessel wall distension, which in turn is determined by the vessel wall transmural pressure. This has been shown experimentally\(^27\) and has been further elaborated by Folkow.\(^19\) The blood pressures of the anesthetized rats in the present study were similar to the ones recorded in the awake rats (untreated SHR, 128 versus 134 mm Hg; perindopril-treated SHR, 98 versus 91 mm Hg). Assuming that the similar perfusion pressures between awake and anesthetized rats translate into similar transmural pressures, we can also assume that the vessels in the two groups of rats were operating close to their normal contractile state. Furthermore, the kidneys in the present study were denervated to avoid effects of reflex changes in renal sympathetic nerve activity that otherwise could have confounded our observations. Nevertheless, different counterregulating mechanisms such as changes in prostaglandin release or shear rate–dependent
release of endothelium-derived vasodilators will still modulate the constrictor response. As shown in Figs 3a and 4a, the response in RBF to both the vasoconstrictors used was qualitatively similar for Ang II and phenylephrine. The reductions in RBF to increasing doses of the two agents were significantly greater in the untreated compared with the ACEI-treated SHR (P<.05). The differences are even more evident when looking at renovascular resistance (P<.05), where the changes are amplified to the fourth power of the radius (Figs 3a and 4a). This finding of less marked RBF and resistance responsiveness in the ACEI-treated group of SHR indicates that ACEI treatment affects the in vivo “vascular resistance amplifier” properties of the renal vasculature.19 We also calculated an average nominal “radius” and conductance for the renal vessels in response to increasing doses of constrictors (see “Methods”). A decreased radius and conductance across the full range of vasoconstrictors has been suggested as the hallmark of the “vascular amplifier” in vivo.13 Both the data for Ang II and phenylephrine showed a significantly greater radius (P<.05) in the ACEI-treated SHR over the full range of vasoconstriction (Fig 3a). The Ang II group also showed a significantly greater conductance over the full range of vasoconstrictors (Fig 3a, P<.05). Thus, when analyzed in this way, it is evident that the vessels in the ACEI-treated group had a larger diameter across the full range of vasoconstriction. Thus, from this in vivo experiment it appears that chronic ACEI significantly affects the in vivo “vascular amplifier” properties, which results in less RBF reduction in response to a given dose of vasoconstrictor agent.

We conclude from these studies that perindopril treatment of SHR increased renovascular diameters, particularly in preglomerular vessels. When considered with our previous morphometric measurements,2 which showed no effect of ACEI on preglomerular arterial wall dimensions, the results suggest that there has been remodeling of the same amount of vessel wall, around a larger lumen diameter (although other changes that affect the mechanical properties of the vessel cannot be ruled out). Such morphological remodeling would be predicted to reduce wall to lumen ratio, which on theoretical grounds would lead to a decrease in the RBF and resistance responsiveness.19 This prediction was confirmed experimentally; there were reduced effects of the two vasoconstrictor agents on RBF in vivo. It is possible that this preglomerular vessel wall remodeling may play a role in the antihypertensive effects of chronic ACEI via the functional effects on renal resistance indicated in this study.

Acknowledgments
The work was supported by the National Health and Medical Research Council of Australia. Dr Bergström was supported by an ISH fellowship of the Foundation for High Blood Pressure Research (Australia), the Swedish Medical Research Council, the Swedish Society of Medicine, and the Swedish Society for Medical Research. At the time of this study, Inger Johansson was a visiting medical student from the University of Göteborg, Sweden.

References
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Hypertension. 1998;31:1007-1013
doi: 10.1161/01.HYP.31.4.1007

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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