Dose-Dependent Effects of Perindopril on Blood Pressure and Small-Artery Structure

Niels K. Thybo, Niels Korsgaard, Susanne Eriksen, Kent L. Christensen, Michael J. Mulvany

Abstract
Long-term treatment of young spontaneously hypertensive rats (SHR) with angiotensin-converting enzyme (ACE) inhibitors has a persistent effect on blood pressure when treatment is withdrawn. The aim of the present study was to determine whether this effect could be mediated by the effect of treatment on resistance-artery structure. We determined the dose dependence of ACE-inhibitor therapy on blood pressure and small-artery morphology during treatment and on the recovery of blood pressure when treatment was withdrawn. SHR (40 per group) were treated from age 4 to 24 weeks with one of three doses of perindopril (0.4, 0.8, or 1.5 mg/kg per day). Control groups were untreated SHR and Wistar-Kyoto rats. At 24 weeks, treatment was stopped and small arteries were taken from half of the rats from the mesenteric, femoral, cerebral, and coronary vascular beds for morphological and functional measurements. The blood pressure of the other half of the rats was followed until 36 weeks of age. During treatment, perindopril caused a dose-dependent reduction in blood pressure and in the media-lumen ratio and media area of the small arteries, whereas there was a dose-dependent increase in lumen diameter. The effect of treatment on the structure of arteries from the different vascular beds was homogeneous. Compared with values from Wistar-Kyoto rats, blood pressure normalization in SHR was not associated with full normalization of structure. After withdrawal of treatment, there was an inverse relation between perindopril dose and the persistent effect. The results suggest that although treatment of SHR has a uniform effect on the structure of small arteries, this effect is not directly related to the persistent effect on blood pressure when treatment is withdrawn. (Hypertension. 1994;23:659-666.)

Key Words • rats, inbred SHR • vascular resistance • blood pressure • antihypertensive agents

Although modern antihypertensive treatment is in general able to control blood pressure, it is almost invariably found that withdrawal of treatment results in blood pressure returning to original hypertensive levels in both essential hypertensive patients1-3 and animal models of hypertension.4-6 A notable exception to this rule concerns treatment of young spontaneously hypertensive rats (SHR) with angiotensin-converting enzyme (ACE) inhibitors, in which, after treatment is discontinued, blood pressure remains at a level below that of control SHR.6-10 This persistent effect of ACE inhibitor treatment seems to be mediated through the ability of ACE inhibitors to reduce angiotensin II levels, for similar results are obtained with the angiotensin II receptor inhibitor losartan.11 There is also evidence that the effect is only seen if the treatment is performed while animals are young.7

Given the fact that the pathogenesis of hypertension in SHR might have relevance for some forms of human essential hypertension, it is clear that elucidation of the mechanism of the persistent effect could provide an interesting new therapeutic approach. One possible mechanism concerns vascular structure because, on the basis that an increased media-lumen ratio of resistance vessels could be a factor that maintains hypertension,12,13 reduction of the media-lumen ratio could maintain low pressure levels. This possibility has been investigated previously by determining whether there was a relation between the effects of different classes of drugs on mesenteric small-artery structure and any persistent effect on blood pressure when treatment was withdrawn.9 The results were negative, in that for those drugs that had similar effects on blood pressure and vascular structure, only the ACE inhibitors had a persistent effect. However, it could be argued that (1) information concerning non–ACE inhibitors is not directly relevant for ACE-inhibitors and (2) the mesenteric small arteries are not representative of the whole vasculature. In the present investigation we have made another approach by using one ACE inhibitor, perindopril, and determining the effect in SHR of three different doses on the structure of small arteries in four vascular beds (mesenteric, femoral, cerebral, and coronary) and how this correlates with the blood pressure both during treatment and after withdrawal of treatment. Untreated Wistar-Kyoto (WKY) rats were also investigated. This approach has allowed us to address the following questions: (1) What are the effects of ACE inhibitor treatment on small-artery structure during treatment? (2) are the effects on small-artery structure similar in different vascular beds? and (3) is the persistent effect of ACE inhibitor treatment on blood pressure related to effects on the structure of small arteries during treatment?

Methods

Animals

Four-week-old male SHR and WKY rats were obtained from the Møllegaard Breeding Centre and kept in pairs in Macrolon cages (0.15 x 0.25 x 0.40 m) with sawdust bedding at
a constant room temperature of 20°C to 21°C and light on from 7 AM to 7 PM.

Medication
Rats were divided into five groups (n=40 in each): untreated WKY rats, untreated SHR, and SHR treated with perindopril doses of 0.4, 0.8, or 1.5 mg/kg per day from the age of 4 to 24 weeks. The drug was administered in drinking water to which the rats had free access, and fresh solutions were prepared once a week. We adjusted the drug concentrations so that the doses (calculated as milligrams per kilogram per day) were kept constant regardless of water intake and body weight. The rats were weighed once a week for the first 2 months and once every 2 weeks thereafter.

Blood Pressure Measurements
Systolic blood pressure (SBP) was monitored by the indirect tail-cuff method, and heart rate was simultaneously recorded. Values were confirmed by intra-arterial measurements as described elsewhere with rats in the resting condition (four to nine rats per group) at ages 24 and 36 weeks.

Dissection and Mounting
At age 24 weeks, 18 to 20 rats in each group were killed under anesthesia with a barbituric acid derivative (Brietial, Eli Lilly & Co), and small-artery segments were isolated from vessels in four different vascular beds: (1) the initial part of the third branch in a mesenteric arcade, (2) the second-generation muscular branch of the left femoral artery passing over the musculus adductor magnus into the gracilis muscle (femoral vessels), (3) the distal part of the left middle cerebral artery before it ramifies on the lateral and dorsal aspect of the cerebral hemisphere, and (4) the segment of the left coronary artery distal to the circumflex ramus. The operators were not aware to which group the animal belonged. Of the remainder, 12 to 14 rats in each group were followed after withdrawal of treatment from 24 to 36 weeks. The small-artery segments were mounted on one of two myographs that were essentially similar to that described previously but were designed so that two segments could be mounted in the same chamber. Experiments were carried out with a femoral and a mesenteric and coronary vessel on one myograph and a mesenteric and coronary artery from the same animal on a second myograph. The vessels were threaded onto two stainless steel wires that were attached to a force transducer and micrometer, respectively. Thus, the myograph performed the direct measurement of vessel isometric wall tension while the internal circumference was controlled. The myograph was mounted on a microscope stage so that the vessel dimensions of mesenteric, femoral, and cerebral arteries could be measured directly. Solutions were changed by draining the chamber and refilling with the new solutions.

It was not possible to determine media thickness of coronary vessels using a light microscope because of difficulty in removing all extracellular tissue, so the following procedure was used for these vessels. At the end of experiments, the vessels were fixed by first holding them in calcium-free physiological salt solution (PSS) for 10 minutes and then changing the chamber solution to prefix (2.5% glutaraldehyde in sodium cacodylate buffer, pH 7.4). The vessels were demounted after at least 30 minutes on the myograph and kept in prefix (4°C) until the remaining fixation procedure could be carried out.

The vessels were then dehydrated, embedded in Historesin (Technovit 7100), and cut longitudinally on a rotation microtome in 4-μm thick sections and stained with Giemsa. On a line-image print of each section, media thickness of the two vessel walls was measured at three different levels. Three measurements per level on each wall were made, and media thickness was then calculated as the mean of all 18 measurements.

Solutions
Vessels were dissected, mounted, and held in PSS of the following composition (mmol/L): NaCl 119, NaHCO3 25, KCl 4.7, KH2PO4 1.18, MgSO4 1.17, CaCl2 2.5, EDTA 0.026, and glucose 5.5. Calcium-free PSS was the same as PSS except that calcium was omitted and 0.1 mmol/L EGTA was included. Activating solutions were K-PSS (as for PSS but with an equimolar exchange of NaCl for KCl), NA-K-PSS (K-PSS containing 10 mmol/L norepinephrine), and 5-HT-PSS (K-PSS containing 10 μmol/L serotonin [5-HT]). All solutions were kept at 37°C, pH 7.4, and bubbled with 5% CO2 in O2. Drugs used were (--) norepinephrine hydrochloride (Sigma Chemical Co) and vasopressin (Sanoflo Pharma Ltd). Perindopril was kindly supplied by Servier Ltd.

Protocol
After dissection and mounting, vessels were equilibrated in calcium-free PSS for approximately 30 minutes. Media thickness was then measured using a light microscope (except for coronary vessels), after which the passive tension–internal circumference relation was determined. The circumference that the vessels would have had in vivo when relaxed and under a transmural pressure of 100 mm Hg was found (Lmax) using Laplace's law: Δp=2xT/l, where Δp is transmural pressure, T is wall tension, and l is effective internal diameter. The vessels were then set to internal circumference L1, where L1=0.9xLmax, and the normalized internal diameter l1 was taken as L1/l. The normalized media thickness at l1 was calculated assuming a constant media volume, and media cross-sectional area was calculated from these parameters. The vessels were equilibrated in PSS for 10 minutes and then stimulated three times in turn with K-PSS, NA-K-PSS, and 5-HT-PSS (2 minutes per activation, 5 minutes between activations).

Calculations and Statistics
The force development was expressed either as active pressure (Δp) on the basis of Laplace's law, Δp=2ΔT/l1, where Δp is the pressure against which the vessel can contract and ΔT is the increase in wall tension on stimulation—or as active media stress, Δm=ΔT/l1, where m is the media thickness at l1. To obtain a general expression for the effect of treatment on vascular morphology, we have combined the values for the four individual beds as follows. In each bed, each parameter was normalized by expressing it relative to the average value obtained in that bed in WKY rats. For each animal, the combined value for each parameter was then taken as the average of the normalized value of that parameter for each of the four vascular beds. Before combining the data from the different vascular beds, we tested for uniformity of variance and of the parameter–blood pressure relations between the different SHR groups and found no significant differences (P>0.05 in all cases).

Effects of treatment between the treated SHR groups were tested with analysis of multiple regression on all SHR (SOLO, BMDP Statistical Software, Inc). Differences in the effect of treatment between the different vascular beds were tested with analysis of multiple regression on two-by-two differences, and differences between other parameters were tested with a one-way ANOVA (Bonferroni test, instat). A value of P<0.05 was considered significant.

Statistical analysis was done only among the SHR, apart from Fig 3, in which the WKY values are compared with the regression lines obtained from the SHR values.

Results
Rat characteristics are given in Table 1. Neither pulse rate nor body weight was much affected by perindopril treatment, although we did find that pulse rate was slightly increased at the lowest dose, and body weight was slightly but significantly decreased at the higher
The withdrawal of treatment, there was an inverse relationship between the perindopril dose and persistent effect. Values are mean±SEM.

Table 1. Data for Study Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>SHR Untreated</th>
<th>Perindopril Dose, mg/kg per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, wk</td>
<td>24</td>
<td>382±12 (20)</td>
</tr>
<tr>
<td>Heart weight, g</td>
<td>24</td>
<td>1,131±7 (13)</td>
</tr>
<tr>
<td>Heart-body weight ratio</td>
<td>24</td>
<td>1,671±6 (14)</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>24</td>
<td>392±10 (37)</td>
</tr>
<tr>
<td>Tall cuff SBP, mm Hg</td>
<td>24</td>
<td>193±3 (37)</td>
</tr>
</tbody>
</table>

Values are mean±SEM for SHR at the end of perindopril treatment (24 weeks) and after 12 weeks withdrawal (36 weeks) compared with untreated SHR and Wistar-Kyoto rats. Numbers of animals are given in parentheses. Comparisons between values in each of the SHR groups were made by one-way ANOVA and Bonferroni test.

*P<.05 (vs untreated); tP<.05 (vs 0.4 mg/kg per day); ||P<.05 (vs 0.8 mg/kg per day).

SHR indicates spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; bpm, beats per minute; and SBP, systolic blood pressure.

The ratio of heart weight to body weight was decreased, but here we found no dose dependence.

**Effect of Treatment on Blood Pressure**

During treatment there was a positive correlation between perindopril dose and the effect on SBP (Table 1). As indicated in Fig 1, SBP was close to or below the WKY value for media cross-sectional area lies above the regression line for the treated SHR. Thus, although not only for SBP but also for DBP and MBP (Table 2).

Compared with the untreated SHR, no significant persistent effect on blood pressure was seen in the group treated with the highest dose.

**Vascular Structure**

Fig 2 shows the morphological measurements of SHR plotted against the SBP of the rats concerned. In each vascular bed, perindopril treatment caused a dose-dependent reduction in the small-artery media-lumen ratio, the dependence on blood pressure appearing to be almost linear (Fig 2a). Treatment also caused a dose-dependent decrease in media cross-sectional area in each of the different vascular beds (Fig 2b), and there was a dose-dependent increase in lumen diameter in all beds (Fig 2c). Multiple regression analysis showed that there was no difference among the four vascular beds as regards the effect of treatment on the media-lumen ratio, media cross-sectional area, and lumen diameter (analysis of multiple regression on two-by-two differences for each parameter; 11<.P<.88).

As described in “Methods,” to obtain a general expression for the effect of treatment on vascular morphology, we combined the values for each parameter in the four different beds by normalizing with respect to the average value measured in that bed for WKY rats. The combined values for each parameter are shown in Fig 3 plotted against SBP. Thus, also for the combined values, the treatment caused a dose-dependent decrease in the media-lumen ratio and media cross-sectional area and a dose-dependent increase in lumen diameter.

Table 3 details the morphological and functional measurements in each of the four vascular beds of the normotensive WKY rats, and the combined values for the WKY vessels, normalized in the same way, are also plotted in Fig 3. It can be seen that as regards the media-lumen ratio, the WKY value lies almost directly on the regression line for the treated SHR. In contrast, the WKY value for media cross-sectional area lies above the regression line for the treated SHR. Thus, although
the untreated combined value of media cross-sectional area for untreated SHR vessels is the same as the WKY value, treatment caused a reduction in small-artery media cross-sectional area. Similarly, the WKY value for lumen diameter lies above the regression line for the treated SHR, such that with reduction of blood pressure to the WKY level, the lumen diameter of the treated SHR vessels is less than that of the WKY vessels.

Functional Vascular Parameters

Table 4 shows the effects of treatment on the function of the small arteries, expressed as active pressure and active media stress (as defined in "Methods"). In mesenteric, femoral, and cerebral resistance arteries, treatment reduced active pressure by approximately 20% but had no significant effect in the coronary arteries. Active media stress showed a tendency to increase with treatment in all vascular beds, although this was only significant for femoral and coronary arteries.

Discussion

Control of Blood Pressure During Treatment

The dose-dependent effect of perindopril on blood pressure—where pressure reduction was maintained throughout treatment, 0.8 mg/kg per day reduced blood pressure to the WKY level, and 1.5 mg/kg per day lowered MBP below WKY values—confirms previous studies on SHR.8,9 Thus, like other ACE inhibitors,4,9,10,19,20 this drug has a strong antihypertensive effect in SHR.

Control of Vascular Structure During Treatment

Media-Lumen Ratio and Lumen Diameter

The dose-dependent decrease in the media-lumen ratio and the dose-dependent increase in lumen diameter observed in this study in the four vascular beds examined are consistent with previous studies of the effect of ACE inhibitor therapy on mesenteric small arteries in SHR.8,9 This suggests that the effect of antihypertensive treatment on the media-lumen ratio and lumen diameter of small arteries may be similar throughout the circulation. The question arises, however, whether these changes are a direct effect of the ACE inhibitor or are consequences of the reduction in blood pressure. Evidence on this question has been provided by three recent investigations using SHR.9,19,20 In these studies, the effect of therapy with ACE inhibitors was compared with hydralazine, and in all cases the ACE inhibitor treatment was found to have a greater effect on the vascular media-lumen ratio. However, in all three cases the ACE inhibitors also had a more potent effect on blood pressure, such that the effect on the media-lumen ratio was correlated with the effect on the blood pressure independent of the type of treatment. Thus, our finding that perindopril caused favorable and consistent dose-dependent changes in the media-lumen ratio and lumen diameter of small arteries in widely spaced areas of the vasculature may be more related to the marked hypotensive action of the drug in these animals than to a drug-specific effect.

Media Cross-sectional Area

Although changes in the media-lumen ratio have frequently been thought of as being synonymous with changes in vascular mass, it has recently been emphasized that these parameters can change independently because of the phenomenon of remodeling.21 With remodeling, the same amount of material can be rearranged around a new lumen diameter, thus causing a change in the media-lumen ratio but without changing media cross section.22 Thus, the conclusion that the effects of perindopril on the media-lumen ratio and lumen diameter may not be due to a specific effect of the drug does not exclude the possibility that the drug could have specific effects on media cross section. Such a specific effect might indeed be expected from a theoretical point of view, because angiotensin II stimulates the growth of vascular smooth muscle cells,23-25 whereas in SHR aorta the ACE inhibitor captopril causes pressure-independent inhibition of media cross-sectional area.26 Therefore, our finding that perindopril causes an inhibition of growth in all of the vascular beds investigated may indicate that these findings also apply

Table 2. Intra-arterial Blood Pressure Measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Age, wk</th>
<th>Untreated</th>
<th>Perindopril Dose, mg/kg per day</th>
<th>SHR</th>
<th>WKY (Untreated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>24</td>
<td>206±4 (9)</td>
<td>165±5* (8)</td>
<td>147±4* (6)</td>
<td>133±4† (7)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>228±8 (4)</td>
<td>195±6 (4)</td>
<td>205±4 (4)</td>
<td>224±9 (4)</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>24</td>
<td>128±4 (9)</td>
<td>103±4 * (8)</td>
<td>97±2* (6)</td>
<td>81±4* (7)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>140±6 (4)</td>
<td>117±4* (4)</td>
<td>120±1* (4)</td>
<td>127±2 (4)</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>24</td>
<td>164±4 (9)</td>
<td>132±4* (8)</td>
<td>122±3* (6)</td>
<td>105±4* (7)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>180±7 (4)</td>
<td>153±5 (4)</td>
<td>150±3 (4)</td>
<td>172±5 (4)</td>
</tr>
<tr>
<td>Pulse rate, bpm</td>
<td>24</td>
<td>334±13 (9)</td>
<td>343±14 (9)</td>
<td>339±15 (6)</td>
<td>371±16 (7)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>375±20 (4)</td>
<td>339±6 (4)</td>
<td>336±12 (4)</td>
<td>348±20 (4)</td>
</tr>
</tbody>
</table>

SHR indicates spontaneously hypertensive rats; WKY, Wistar-Kyoto rats; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; and bpm, beats per minute. Values are mean±SEM for SHR at the end of perindopril treatment (24 weeks) and after 12 weeks withdrawal (36 weeks) compared with untreated control SHR and WKY. Numbers of animals are given in parentheses. Statistical comparison by one-way ANOVA and Bonferroni.

*P<.05 (vs untreated); †P<.05 (vs 0.4 mg/kg per day); ||P<.05 (vs 0.8 mg/kg per day); all SHR groups tested against each other. *P<.05 difference to untreated SHR (treated SHR groups tested against untreated SHR group).
Effect of Treatment on SHR Vessels

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**Effect of Treatment on SHR Vessels**

![Graphs showing vascular structure of mesenteric, femoral, cerebral, and coronary small arteries from spontaneously hypertensive rats (n=15-20 per group) treated with perindopril (0 [●], 0.4 [●], 0.8 [●], and 1.5 [●] mg/kg per day).](http://hyper.ahajournals.org/)

**FIG 2.** Line graphs show vascular structure of mesenteric, femoral, cerebral, and coronary small arteries from spontaneously hypertensive rats (n=15-20 per group) treated with perindopril (0 [●], 0.4 [●], 0.8 [●], and 1.5 [●] mg/kg per day). a, Media-lumen ratio vs systolic blood pressure. In all cases there was a dose-dependent decrease in media-lumen ratio. b, Media cross-sectional area vs systolic blood pressure. In all cases there was a dose-dependent decrease in media cross-sectional area, although it was not significant for coronary vessels. c, Lumen diameter vs systolic blood pressure. In all cases there was a dose-dependent increase in lumen diameter, although it was not significant (P=.055) for coronary vessels. Lines show regression for individual values obtained from all animals. Asterisks show significance for difference of slopes of regression lines from zero (*P<.05, **P<.01, ***P<.001). Analysis of multiple regression showed no difference in the effect of treatment on any of parameters a, b, or c among the different vascular beds. Values are mean±SEM.

**Effect of Treatment Compared With WKY Rats**

It has been a common finding in hemodynamic studies in essential hypertensive patients that even effective antihypertensive treatment is not able to normalize vascular structure, as expressed by minimum forearm (or hand) resistance.27,28 These findings have been supported by in vitro examination of small arteries from treated essential hypertensive patients29 as well as rat studies using the WKY rat as a control.9,30 Such failure to normalize vascular structure could have serious therapeutic consequences, because clearly, normalization of blood pressure without a proportional increase in lumen diameter will lead to an inappropriate decrease in blood flow. One could therefore speculate that the apparent failure to achieve complete normalization of vascular structure could be part of the explanation for the relatively disappointing effect of antihypertensive treatment on cardiac events.31

In the present investigation we also found that although the media-lumen ratio was fully normalized compared with WKY rats (Fig 3), neither lumen diameter nor media cross-sectional area was normalized. Indeed, on average, media cross-sectional area was the same in SHR and WKY rats (Fig 3), so the dose-dependent reduction in media cross-sectional area caused by the perindopril treatment appears to be creating an abnormality, one that could be part of the reason for the failure of lumen diameter to be normalized. However, given the doubt now raised about the suitability of the WKY rat as a control for the SHR,32 this conclusion may be questioned.
TABLE 3. Morphological and Functional Properties of Resistance Arteries Taken From 24-Week-Old Untreated Wistar-Kyoto Rats

<table>
<thead>
<tr>
<th>Vascular Bed</th>
<th>n</th>
<th>Lumen, μm</th>
<th>Media, μm</th>
<th>Media-Lumen Ratio, %</th>
<th>Area, μm²x10²</th>
<th>Active Pressure, kPa</th>
<th>Active Stress, kPa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesenteric</td>
<td>17</td>
<td>245±12</td>
<td>13.8±1.1</td>
<td>6.56±0.73</td>
<td>10.3±0.8</td>
<td>25.5±1.4</td>
<td>222±21</td>
</tr>
<tr>
<td>Femoral</td>
<td>18</td>
<td>227±8</td>
<td>19.6±1.6</td>
<td>10.15±1.08</td>
<td>13.9±1.0</td>
<td>35.7±1.8</td>
<td>203±18</td>
</tr>
<tr>
<td>Cerebral</td>
<td>19</td>
<td>247±6</td>
<td>13.8±0.8</td>
<td>6.31±0.48</td>
<td>10.4±0.6</td>
<td>20.9±1.1</td>
<td>172±9</td>
</tr>
<tr>
<td>Coronary</td>
<td>16</td>
<td>319±20</td>
<td>22.4±1.2</td>
<td>8.16±0.62</td>
<td>22.1±2.2</td>
<td>19.7±1.8</td>
<td>127±9</td>
</tr>
</tbody>
</table>

Values are mean±SEM.
forms of hypertension could have a long-term beneficial effect. Unfortunately, however, this provocative speculation can hardly be tested directly.

In conclusion, the data show that during treatment with perindopril there was a dose-dependent effect on blood pressure and on the structure of small arteries in four different vascular beds. In all cases, lumen diameter increased, the media-lumen ratio decreased, and media cross-sectional area decreased. Importantly, the effect of treatment with perindopril on resistance arteries from different vascular beds appeared identical. A persistent effect on blood pressure was observed after withdrawal of treatment, the effect being most marked in those rats that had received the lowest dose of perindopril.

Acknowledgments

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References

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