Endothelial Dysfunction and Subendothelial Monocyte Macrophages in Hypertension
Effect of Angiotensin Converting Enzyme Inhibition

Martine Clozel, Herbert Kuhn, Fridolin Hefti, and Hans R. Baumgartner

Hypertension is associated with an impairment of endothelium-dependent relaxation. The angiotensin converting enzyme inhibitors captopril and cilazapril can prevent this endothelial dysfunction. We recently observed that long-term treatment with cilazapril could also prevent subendothelial infiltration by mononuclear cells in spontaneously hypertensive rats. This prompted us to examine whether, in spontaneously hypertensive rats, endothelial dysfunction and subendothelial infiltration by mononuclear cells are associated. These cells were characterized as monocyte macrophages. Infiltration by monocyte macrophages was quantified by morphometry. Endothelial function was estimated by calculating serotonin ratio (maximal contraction to serotonin on isolated arterial rings with endothelium over maximal contraction on paired rings without endothelium). The regional distribution of endothelial dysfunction and subendothelial monocyte macrophages was similar. Both were maximal in the carotid artery, less in the aorta, and nonexistent in the renal artery. A 2-week treatment with cilazapril decreased both endothelial dysfunction (serotonin ratio decreased by 32%) and the number of subendothelial monocyte macrophages in the aorta, which decreased by 38%. We conclude that in spontaneously hypertensive rats, endothelial dysfunction and subendothelial monocyte macrophage infiltration are associated and that cilazapril can decrease both. The observation that angiotensin converting enzyme inhibitors affect subendothelial accumulation of monocyte macrophages may lead to a better understanding of the mechanism of action of this class of drugs. (Hypertension 1991;18:132–141)

Endothelium-dependent responses are altered in hypertension. Acetylcholine1-2 and serotonin3 can induce endothelium-dependent contractions in spontaneously hypertensive rats (SHR) but not in Wistar-Kyoto (WKY) rats. In dogs, acute hypertension provokes an endothelium-dependent potentiation of the coronary vasoconstrictor response to serotonin.4

Endothelium-dependent relaxation is impaired in SHR and stroke-prone SHR,3,5,6 but endothelium-independent relaxation is not.6-8 Similar endothelial dysfunction has also recently been shown in human hypertension.9,10 The endothelial vasoconstrictor substance produced in excess during hypertension is a product of the cyclooxygenase pathway2-6,7,11 and is likely to be a prostaglandin endoperoxide such as prostaglandin H2 since its action is inhibited by thromboxane/endoperoxide receptor antagonists, but its synthesis is not blocked by thromboxane synthetase inhibitors.12-14 In a previous paper, we have shown that a 4-month treatment with the angiotensin converting enzyme (ACE) inhibitor cilazapril, but not with the pure vasodilator hydralazine, was able to prevent endothelial dysfunction in SHR.15 In addition, we described for the first time another effect of an ACE inhibitor: in carotid arteries of SHR the invasion of the subendothelium by mononuclear cells with the ultrastructural characteristics of monocyte macrophages was completely prevented by cilazapril. From this finding, it was tempting to speculate that endothelial dysfunction in SHR was caused by or associated with subendothelial infiltration of monocyte macrophages. The present study was therefore designed to evaluate the association between the presence of monocyte macrophages and the endothelial dysfunction. For this purpose, we examined the regional distribution of monocyte macrophage infiltration and of endothelial dysfunction. In addition we determined whether the beneficial effect of a short-term treatment with an ACE inhibitor on endothelial function was associated with a decrease in subendothelial monocyte macrophages.
Animals

Male 18- to 24-week-old SHR and, in some experiments, age-matched WKY rats were used. All rats were housed in similar conditions and had free access to water.

Immunofluorescent Staining on Whole Arteries

The rats were anesthetized with ether and exsanguinated. Segments of thoracic aorta, carotid arteries, and renal arteries were excised. Cryostat sections 8 μm thick were obtained and fixed for 30 minutes in 4% paraformaldehyde. A monoclonal mouse antibody against rat monocyte macrophages (ED1, Serotec, Oxford, England) at a concentration of 1:100 in phosphate-buffered saline was applied for 20 minutes. ED1 is specific for rat monocyte macrophages and does not recognize granulocytes, lymphocytes, endothelial cells,16 or smooth muscle cells. Fluorescein-conjugated goat anti-mouse antibody (Dakopatts, Glostrup, Denmark) was used as a second antibody at a concentration of 1:40.

Morphological Evaluation of Monocyte Macrophage Infiltration on Whole Arteries

The rats were anesthetized with sodium pentobarbital (Nembutal, Abbott Laboratories, North Chicago, Ill.), and a catheter was inserted in the abdominal aorta. The rat was then perfused at a pressure of 120 mm Hg, first with 5 ml Krebs-Henseleit solution containing 10^{-3} M adenosine, then with 2.5% glutaraldehyde buffered with 0.1 M phosphate buffer (pH 7.4, 4°C). After washing with 0.1 M sodium cacodylate buffered with 0.1 M phosphate buffer (pH 7.4, room temperature) for 15 minutes, the descending thoracic aorta, common carotid artery, and renal arteries were excised, dissected, and cut in 5-mm rings. Two rings were used for each rat: in one ring the endothelium was left intact, in the other the endothelium was removed by gentle rubbing of the intimal surface. In rings studied in parallel, the presence or absence of endothelium was checked by morphological evaluation after Evans blue staining. The rings without endothelium showed a homogenous blue staining of their inner surface. Each ring was suspended in a 10 ml isolated organ bath filled with Krebs-Henseleit solution (in mM) (NaCl 115, KCl 4.7, MgSO_{4} 1.2, KHPO_{4} 1.5, NaHCO_{3} 25, CaCl_{2} 2.5, glucose 11.1) that was kept at 37°C and gassed with a 95% O_{2}-5% CO_{2} mixture. The rings were connected to force transducers and isometric tension was recorded (recorder Lin Recordex mark VII, Graphtec Corp., Tokyo).

The rings were stretched to a resting tension of 3 g. After an equilibration period, the rings were exposed repetitively to 10^{-7} M norepinephrine until a maximal response was obtained. On the rings where the endothelium had been rubbed, the absence of endothelium was confirmed by the absence of relaxation to 10^{-5} M acetylcholine. After the rings had been washed and returned to a stable baseline, the constricting effect of serotonin was evaluated on all the rings by adding cumulative doses of serotonin (10^{-8} to 10^{-4} M). The concentration of serotonin exhibiting 50% maximal contraction (EC_{50}) was calculated and the maximal contraction was measured. In addition, the ratio of the maximal contraction of a ring with endothelium over the maximal contraction of a ring without endothelium from the same rat ("serotonin ratio") was calculated.

In other experiments, the common carotid arteries and the left renal artery were excised, dissected, and cut into rings. For the carotid artery, two rings, one with intact endothelium and one without endothelium, were used for each rat, exactly as for the thoracic aorta. For the renal artery, only one ring per rat was used, but in each experiment, rings with and rings without endothelium were always studied in parallel. The resting tension was adjusted to 2 g for carotid arteries and 1 g for renal arteries. These tensions had been shown in preliminary experiments to be the optimal point of the length–tension relation in both SHR and WKY rats. After an equilibration period, the rings were exposed to norepinephrine. The presence or absence of a functional endothelium was assessed by the presence or absence of relaxation to acetylcholine (10^{-5} M). In the renal artery, the

Methods

Animals

Male 18- to 24-week-old SHR and, in some experiments, age-matched WKY rats were used. All rats were housed in similar conditions and had free access to water.
Macrophage Infiltration was confirmed by light microscopy and morphological evaluation. Light micrographs from arteries fixed in a relaxed state after adenosine infusion showed that in the aorta of SHR, endothelial cells are separated from the IEL by a thickened subendothelium (Figure 2A). This is even more the case in the carotid artery of SHR where the subendothelium becomes extremely thick (Figure 2B). In contrast, in the renal artery, endothelial cells seem directly in contact with IEL (Figure 2C). In WKY rats, the subendothelium is hardly visible in all three arteries (Figures 2D, 2E, and 2F). The number of cell nuclei per millimeter IEL in the subendothelium of SHR was maximal in the carotid artery, less in the aorta, very low in the renal artery, and was very low in all arteries of WKY rats (Table 1). Figure 2 also clearly shows the marked thickening of the smooth muscle cells and of the elastin layers in the media of SHR, especially in the carotid and renal arteries.

**Regional Distribution of Endothelial Dysfunction**

Endothelial function was estimated in aorta, carotid artery, and renal artery of SHR and WKY rats by comparing the concentration–response curves of serotonin on rings with intact and without endothelium (Figure 3). In the carotid artery, the maximal response to serotonin was similar in both strains in the absence of endothelium but much greater in SHR in the presence of endothelium. In the aorta, the maximal response to serotonin was smaller in SHR than WKY rats in the absence of endothelium. This was reversed in the presence of endothelium. Finally, in the renal artery the response was similar in SHR and WKY rats in the presence and in the absence of endothelium. An estimate of endothelial function was derived from these curves by calculation of the serotonin ratio. This ratio was significantly higher in SHR than in WKY rats in the aorta and carotid artery but not in the renal artery (Table 2). The relative difference between serotonin ratios in SHR and WKY rats was maximal in the carotid artery (+179%, \( p<0.001 \)), less in the aorta (+64%, \( p<0.001 \)), and virtually nil in the renal artery (−2%).

**Effect of Short-term Cilazapril Treatment on Monocyte Macrophage Infiltration and Endothelial Dysfunction**

In SHR treated with cilazapril, systolic blood pressure decreased from 218±5 mm Hg before treatment \((n=16)\) to 150±4 mm Hg \((n=16)\) and 131±2 mm Hg \((n=16)\) after 2 and 4 weeks of cilazapril, respectively. Body weight remained stable \((323±5 \text{ g}, 325±7 \text{ g}, \text{ and } 321±3 \text{ g})\) respectively, before and after 2 and 4 weeks of cilazapril.

Cilazapril decreased to a marked extent the subendothelial infiltration of monocyte macrophages. As seen in Figure 4 and Table 3, the thickness of the subendothelium in the carotid artery decreased markedly after 2 weeks and even further after 4 weeks of treatment. The number of subendothelial cell nuclei per cross section decreased by 61% at 2 and 4 weeks (Table 3). Cilazapril decreased significantly the length of IEL. Despite that, it decreased...
FIGURE 1. Photomicrograph shows immunofluorescent staining with anti-rat monocyte macrophage antibody EDI of aorta (panels a, d), carotid artery (panels b, e), and renal artery (panel c) of spontaneously hypertensive rats (SHR) (panels a-c) and Wistar-Kyoto (WKY) rats (panels d, e). Note presence of stained monocyte macrophages in intima of aorta and carotid arteries of SHR only (panels a, b). Faint staining of elastic layers in media corresponds to a nonspecific staining by fluorescein-conjugated goat anti-mouse antibody. Panel f: Control experiment made on SHR aorta in absence of EDI. Note absence of staining of monocyte macrophages.

also significantly the number of cell nuclei per millimeter IEL and not only the absolute number of cell nuclei per cross section. However, it had no significant effect on the surface coverage of IEL by thickened subendothelium (Table 3). In the aorta, only the number of subendothelial cell nuclei and the length of IEL were evaluated. Because of the ill-defined and often splitted IEL, it was not possible to estimate accurately the cross-sectional surface area of the subendothelium or the surface coverage. In the aorta, cilazapril decreased the number of subendothelial cell nuclei by 38% (p<0.05) and 40% (p<0.05) after 2 and 4 weeks, respectively, but it had no significant effect on the length of IEL.

Cilazapril did not only decrease the number of monocyte macrophages in the subendothelium but also had a remarkable effect for improving endothelial function in aorta of SHR. The endothelial part of the contractions induced by serotonin was markedly reduced by cilazapril. In the absence of endothelium, the maximal contraction to serotonin was slightly, but not significantly, affected by cilazapril. In contrast, in the presence of endothelium, the maximal contraction was decreased by up to 52% by cilazapril (Figure 5). Accordingly the serotonin ratio decreased from 1.17±0.04 before cilazapril to 0.80±0.06 (p<0.001) and 0.65±0.05 (p<0.001) after 2 and 4 weeks of treatment, respectively (Figure 6). The effect of cilazapril on serotonin ratio was significantly greater after 4 weeks than 2 weeks (p<0.05).

Discussion

Our results show that in SHR, among the three arteries examined, endothelial function was altered in aorta and carotid artery, where subendothelium was infiltrated with monocyte macrophages but was not altered in the renal artery where subendothelium was almost free of monocyte macrophage infiltration.
Our results thus suggest an association between the presence of monocyte macrophages in subendothelium and endothelial dysfunction in SHR.

In the comparison between SHR and WKY rats, endothelial function was estimated by the calculation of the ratio of the maximal contraction to serotonin of intact rings (smooth muscle + endothelium) over the maximal contraction to serotonin of deendothelialized rings (smooth muscle "alone"). This "serotonin ratio" enables us to abstract the smooth muscle reactivity since the smooth muscle appears in both terms of the ratio. Serotonin ratio is therefore not affected by a change in smooth muscle reactivity. It reflects the moderating role (if the ratio is less than 1) or the potentiating role (if the ratio is greater than 1) of the endothelium in the contraction induced by serotonin. Our results show that the moderating role of the endothelium, which was extremely marked in the carotid artery (serotonin ratio of 0.38 ±0.08) and less pronounced in the aorta (serotonin ratio of 0.70 ±0.04) of WKY rats, was reversed into a potentiating role (serotonin ratio over 1) in SHR. The difference between SHR and WKY rats was much greater in the carotid artery than in the aorta, indicating that the magnitude of endothelial dysfunction in SHR was greater in the carotid artery than in

### Table 1. Number of Subendothelial Cell Nuclei per Millimeter Internal Elastic Lamina in Aorta, Carotid Artery, and Renal Artery of Spontaneously Hypertensive Rats and Wistar-Kyoto Rats

<table>
<thead>
<tr>
<th>Artery</th>
<th>WKY</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery</td>
<td>0.6±0.3</td>
<td>8.1±1.1</td>
</tr>
<tr>
<td>Aorta</td>
<td>0.8±0.3</td>
<td>4.5±0.6</td>
</tr>
<tr>
<td>Renal artery</td>
<td>0.4±0.2</td>
<td>0.7±0.2</td>
</tr>
</tbody>
</table>

For aorta and carotid artery from spontaneously hypertensive rats (SHR), the rats of the control group of the cilazapril study were used (see Table 3). For renal artery from SHR, another set of rats was used. Number of animals is indicated in parentheses.

IEL, internal elastic lamina; WKY, Wistar-Kyoto rats.

*p<0.001 compared with WKY rats.
the aorta. These findings are consistent with the fact that in SHR, serotonin can induce the release of an endothelium-derived constricting factor in aorta3 and cerebral arteries5-6,17 whereas in WKY rats the action of serotonin is modulated by the release of endothelium-derived relaxing factor (EDRF).17,18 This endothelium-derived constricting factor produced in SHR on administration of serotonin or acetylcholine is likely to be the unstable prostaglan-

din endoperoxide prostaglandin H₂.12-14 In contrast, we found no difference between SHR and WKY rats in the serotonin ratio on renal arteries, showing that there is no endothelial dysfunction in renal arteries of SHR. Moreover, we found that the serotonin ratio was close to 1 in renal arteries of WKY rats. This suggests that, even in WKY rats, the moderating effect of the endothelium is virtually absent in the renal artery. These findings are consistent with a previous report by Lüscher et al.17

Morphological evaluation of the three arteries showed a regional distribution of the subendothelial infiltration with monocyte macrophages similar to the regional distribution of endothelial dysfunction. Indeed, the number of subendothelial cell nuclei in SHR was highest in the carotid artery, less in the aorta, and very low in the renal artery. In WKY rats, the number of subendothelial cell nuclei was very low in all three arteries. The presence of mononuclear cells in the subendothelium of hypertensive rats had already been described in the aorta after acute19,20 or chronic hypertension,21-25 and Chobanian et al.26 had described an increase in blood cell adherence to aortic endothelium in hypertension. Our study allows the characterization of these mononuclear cells as monocyte macrophages and gives for the first time a

**Table 2. Ratio of Maximal Tension Induced by Serotonin on Rings With Endothelium Over Maximal Tension on Rings Without Endothelium in Aorta, Carotid Artery, and Renal Artery of Spontaneously Hypertensive Rats and Wistar-Kyoto Rats**

<table>
<thead>
<tr>
<th>Artery</th>
<th>WKY rats</th>
<th>SHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery</td>
<td>0.38±0.08 (8)</td>
<td>1.06±0.05 (8)*</td>
</tr>
<tr>
<td>Aorta</td>
<td>0.70±0.04 (8)</td>
<td>1.15±0.08 (8)*</td>
</tr>
<tr>
<td>Renal artery</td>
<td>1.11 (8)</td>
<td>1.09 (8)</td>
</tr>
</tbody>
</table>

For aorta and carotid artery, serotonin ratio was calculated for each rat and mean±SEM was calculated. For renal artery, where only one ring per rat was used, serotonin ratio was calculated from the mean values of the maximal responses to serotonin and not from the individual data. Number of animals is indicated in parentheses. WKY, Wistar-Kyoto rats; SHR, spontaneously hypertensive rats.

*p<0.001 compared with WKY rats.
quantitative evaluation of the heterogeneity of their regional distribution. Our data do not rule out the possibility that some of the subendothelial cells may be of another cell type (i.e., lymphocytes or smooth muscle cells). However, the concurrence of light microscopy, electron microscopy, and immunofluorescence indicates that most cells are actually monocyte macrophages. It is striking to see that these monocyte macrophages are present in the aorta and carotid artery but virtually absent in the renal artery.

### Table 3. Morphological Evaluation of Effect of Cilazapril on Monocyte Macrophage Infiltration in Subendothelium of Carotid Artery and Aorta of Spontaneously Hypertensive Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (7)</th>
<th>Cilazapril 2 weeks (8)</th>
<th>Cilazapril 4 weeks (8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subendothelial area (μm²)</td>
<td>6,771±927</td>
<td>2,846±534*</td>
<td>1,610±228*</td>
</tr>
<tr>
<td>Coverage of IEL by thickened subendothelium (%)</td>
<td>75.7±6.3</td>
<td>62.0±9.8</td>
<td>54.5±7.1</td>
</tr>
<tr>
<td>Cell nuclei per cross section (n)</td>
<td>16.9±2.4</td>
<td>6.6±1.1†</td>
<td>6.6±1.6†</td>
</tr>
<tr>
<td>Cell nuclei per mm IEL (n)</td>
<td>8.1±1.1</td>
<td>3.4±0.6†</td>
<td>3.8±0.9†</td>
</tr>
<tr>
<td>Length of IEL (mm)</td>
<td>2.06±0.06</td>
<td>1.96±0.02</td>
<td>1.78±0.05†</td>
</tr>
<tr>
<td>Aorta</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cell nuclei per cross section (n)</td>
<td>25.0±3.3</td>
<td>15.4±1.9‡</td>
<td>14.9±2.2‡</td>
</tr>
<tr>
<td>Cell nuclei per mm IEL (n)</td>
<td>4.5±0.6</td>
<td>2.9±0.4‡</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>Length of IEL (mm)</td>
<td>5.52±0.16</td>
<td>5.38±0.10</td>
<td>5.16±0.15</td>
</tr>
</tbody>
</table>

Cross-sectional surface area of subendothelium, surface coverage of internal elastic lamina (IEL) by thickened subendothelium, and number of subendothelial cell nuclei per cross section and per millimeter IEL were evaluated by morphometry. In aorta only the number of subendothelial cell nuclei was estimated. Number of animals is indicated in parentheses. One rat in the control group died just before the experiment.

* p<0.001, † p<0.01, ‡ p<0.05 compared with control before cilazapril.
Cilazapril decreased the length of IEL. This decrease was exactly the same as after 4 months of treatment. The effect was similar at 2 and 4 weeks. Moreover, turned to the blood on cilazapril treatment. The section indicates that monocyte macrophages infiltration after short-term cilazapril treatment in SHR. Cilazapril decreased the endothelial part of the subendothelial infiltration with monocyte macrophages in aorta of spontaneously hypertensive rats (SHR) before (control) and after 2 and 4 weeks of cilazapril. ***p<0.001 compared with control.

All three arteries are capacitance arteries. Therefore, rheologic parameters such as shear stress, which is known to influence leukocyte adhesion to endothelial cells,27 do not differ sufficiently to explain such a regional distribution. Instead, this heterogeneity suggests that the trigger of the adhesion of monocyte macrophages to endothelium stems from the vascular wall. Because endothelial dysfunction and monocyte macrophage infiltration appear to be associated, one could speculate that an early event in hypertension might be endothelial “activation,” leading both to increased adherence and chemotaxis of monocytes and to abnormal production of an endothelium-derived constricting factor. Alternatively, the monocyte macrophages might themselves secrete constricting factors or further activate endothelial cells. Future studies should be designed to determine the link between endothelial dysfunction and monocyte macrophage infiltration.

In addition to the association between endothelial dysfunction and the presence of subendothelial monocyte macrophages in SHR, our results show the association between improvement of endothelial function and decrease of monocyte macrophage infiltration after short-term cilazapril treatment in SHR. Cilazapril decreased the endothelial part of the contractions induced by serotonin in SHR aorta, as shown by the decrease in serotonin ratio. The effect of cilazapril on endothelial function in SHR aorta was already pronounced after 2 weeks of treatment and was further increased after 4 weeks. After 4 weeks of cilazapril, the value of the serotonin ratio was exactly the same as after 4 months of treatment.15 In parallel, cilazapril decreased the subendothelial infiltration with monocyte macrophages in both aorta and carotid artery. The decrease in absolute amount of subendothelial cell nuclei per cross section indicates that monocyte macrophages returned to the blood on cilazapril treatment. The effect was similar at 2 and 4 weeks. Moreover, cilazapril decreased the length of IEL. This decrease in length of IEL could be due to adaptation of the vessel to low blood pressure or to a decrease in elastin content. Hypertension is known to be associated with an increased synthesis of arterial elastin, collagen, and fibronectin.21,22,26,29 Cilazapril might have an effect not only on monocyte macrophages but also on noncellular elements in the intima.

We can speculate that the effects of cilazapril on endothelial function and monocyte macrophage infiltration might be common to other ACE inhibitors. Another ACE inhibitor of different chemical structure, captopril, was also shown to improve endothelial function in SHR.15 The effects of ACE inhibitors on endothelial dysfunction are probably not due solely to their blood pressure–lowering effect since hydralazine, a pure vasodilator, had no effect on endothelial dysfunction in SHR.15 Indeed, ACE inhibitors might have a more specific mechanism of action. They decrease the degradation of bradykinin, which is a stimulant of EDRF production30 and might therefore increase the synthesis or release of EDRF. They might also interfere with eicosanoid metabolism, either by increasing the synthesis or release of a vasodilator prostaglandin31 or by decreasing the synthesis or release of the abnormal vasoconstrictor prostaglandin H₂. This latter hypothesis is unlikely because we had shown in a previous publication that the effect of indomethacin for normalizing the serotonin ratio was preserved in cilazapril-treated SHR, suggesting that the mechanism of action of cilazapril was not the same as indomethacin.15 Cilazapril and other ACE inhibitors have also been shown to reduce the increased thickness of the media in various arteries of SHR.32,33 Serotonin ratio is not affected by a change in smooth muscle reactivity but might possibly be affected by a change in the diffusion of endothelium-derived factors between intima and media. It is, however, unlikely that the beneficial effect of cilazapril on endothelial function might solely be due to an increased capacity of EDRF to reach the smooth muscle.

The improvement in endothelial function afforded by cilazapril might be responsible for the decrease of monocyte macrophage infiltration because quiescent endothelial cells inhibit leukocyte adherence and chemotactic activity.34 On the other hand, the primary effect of cilazapril might be to inhibit monocyte macrophage infiltration by some yet unknown mechanism (such as blood pressure lowering or ACE inhibition) and to prevent secondary endothelial dysfunction.

Endothelial dysfunction and infiltration with monocyte macrophages are not only associated in hypertension but also in aging14,35 and atherosclerosis.26-29 Hypertension favors atherosclerosis,40 and one can speculate that both endothelial dysfunction and the subendothelial monocyte macrophages might participate in the development of atherosclerosis. It is striking to note that endothelial dysfunction and monocyte macrophages infiltration in hypertension...
are found in large vessels that are actually the site of predilection of atherosclerotic lesions.\textsuperscript{41}

The effects of cilazapril on both endothelial dysfunction and monocyte macrophage infiltration suggest that ACE inhibitors might be useful in the prevention of atherosclerosis. The recent publication describing a beneficial effect of captopril on atherogenesis in Watanabe heritable hyperlipidemic rabbit\textsuperscript{42} is in favor of this hypothesis.

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38. Werns SW, Walton JA, Hisia HH, Nabel EG, Sanz ML, Pitt B: Evidence of endothelial dysfunction in angiographically nor-

**KEY WORDS** • chronic hypertension • rat studies • monocyte macrophages • cilazapril • angiotensin converting enzyme inhibitor • endothelium


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36. mal coronary arteries of patients with coronary artery disease.

35. Early and/or rapid suppression of plasma renin activity by cilazapril.

34. Cilazapril delayed progression of early atherosclerotic plaques.

33. By 20% and 40% at 4 and 8 weeks, respectively.

32. Angiotensin-converting enzyme inhibitors.

31. Other endothelial cells such as fibroblasts have similar effects.

30. In the presence of atherogenic lipids.

29. Angiotensin-converting enzyme (ACE)

28. from the aorta to the coronary arteries.

27. Monocyte Macrophages in Hypertension


25. Cilazapril inhibited the proliferation of cultured smooth muscle cells.

24. Cilazapril decreased the progression of carotid atherosclerosis.

23. Cilazapril reduced the severity of atherosclerosis in diabetic rats.

22. Cilazapril reduced the progression of early atherosclerotic plaques.


20. Cilazapril had no effect on the progression of early atherosclerotic plaques.

19. Cilazapril reduced the progression of atherosclerosis in diabetic rats.

18. Cilazapril decreased the progression of early atherosclerotic plaques.

17. Cilazapril reduced the progression of atherosclerosis in diabetic rats.

16. Cilazapril decreased the progression of early atherosclerotic plaques.

15. Cilazapril reduced the progression of early atherosclerotic plaques.

14. Cilazapril decreased the progression of early atherosclerotic plaques.

13. Cilazapril decreased the progression of early atherosclerotic plaques.

12. Cilazapril decreased the progression of early atherosclerotic plaques.

11. Cilazapril decreased the progression of early atherosclerotic plaques.

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9. Cilazapril decreased the progression of early atherosclerotic plaques.

8. Cilazapril decreased the progression of early atherosclerotic plaques.

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6. Cilazapril decreased the progression of early atherosclerotic plaques.

5. Cilazapril decreased the progression of early atherosclerotic plaques.

4. Cilazapril decreased the progression of early atherosclerotic plaques.

3. Cilazapril decreased the progression of early atherosclerotic plaques.

2. Cilazapril decreased the progression of early atherosclerotic plaques.

1. Cilazapril decreased the progression of early atherosclerotic plaques.
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