Inhibition of Early Atherogenesis by Losartan in Monkeys With Diet-Induced Hypercholesterolemia

William B. Strawn, DVM, PhD; Mark C. Chappell, PhD; Richard H. Dean, MD; Salah Kivlighn, PhD; Carlos M. Ferrario, MD

Background—Angiotensin II may contribute to atherogenesis by facilitating the proliferative and inflammatory response to hypercholesterolemia. This study determined, in a primate model of diet-induced atherosclerosis, the effect of AT₁ blockade on fatty-streak formation, plasma lipids, and surrogate markers of vascular injury.

Methods and Results—Male cynomolgus monkeys fed a diet containing 0.067 mg cholesterol/kJ for 20 weeks were given losartan (180 mg/d, n=6) or vehicle (n=8) for 6 weeks starting at week 12 of the dietary regimen. Arterial pressure, heart rate, plasma total and lipoprotein cholesterol concentrations, and lipoprotein particle sizes and subclass distributions were unaffected by treatment. Losartan caused significant (P<0.05) increases in plasma angiotensin II and angiotensin-(1–7). Compared with vehicle-treated controls, losartan reduced the extent of fatty streak in the aorta, the coronary arteries, and the carotid arteries by ∼50% (P<0.05). A significant (P<0.05) reduction in the susceptibility of LDL to in vitro oxidation, serum levels of monocyte chemoattractant protein-1, and circulating monocyte CD11b expression were also associated with losartan treatment. In addition, serum levels of vascular cell adhesion molecule-1 and E-selectin did not change during treatment but increased after discontinuation of losartan. Serum C-reactive protein, platelet aggregability, and white cell counts were not modified by losartan.

Conclusions—This study demonstrates for the first time an antiatherogenic effect of AT₁ receptor blockade in nonhuman primates. Losartan inhibited fatty-streak formation through mechanisms that may include protection of LDL from oxidation and suppression of vascular monocyte activation and recruitment factors. (Circulation. 2000;101:1586-1593.)

Key Words: atherosclerosis ■ angiotensin ■ cell adhesion molecules ■ hypercholesterolemia ■ lipoproteins

The evolution of atherosclerosis may be influenced by actions of angiotensin II (Ang II) on endothelial function, 1,2 monocyte activation and binding, 3 vascular smooth muscle cell proliferation and migration, 4 and oxidation of LDL. 5 Detection of ACE and Ang II in human atheroma suggests a role for angiotensin peptides in atherogenesis. 6 Arterial deposition of oxidized LDL is stimulated by Ang II, and compared with native LDL, Ang II–modified LDL interacts with macrophage scavenger receptors at an enhanced rate. 7 Furthermore, Ang II activates circulating monocytes, adhesion molecules, and cytokines. 8 These findings suggest that Ang II may contribute to the vascular inflammatory response observed in early diet-induced atherosclerosis.

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Hypercholesterolemia-induced atherosclerosis in cynomolgus monkeys, which bears marked similarities to the disease in humans, 8 is inhibited by the administration of ACE inhibitors. 9 To more directly evaluate the role of Ang II in atherogenesis, we investigated whether AT₁ receptor blockade retards atherogenesis in this species by measuring the extent of fatty-streak formation, lipoprotein atherogenicity, the activation status of circulating monocytes and platelets, and levels of circulating adhesion molecules.

Methods

Animals and Experimental Protocol

Twenty adult male cynomolgus (Macaca fascicularis) monkeys (weight, 4 to 7 kg) were fed an atherogenic diet containing 0.067 mg cholesterol/kJ for 20 weeks. The diet was prepared on site and given to the animals once daily at the same time each day. Water was available ad libitum. Surgical procedures were done under sterile conditions after induction of anesthesia with ketamine hydrochloride (40 mg/kg IM, Fort Dodge Laboratories). All procedures were performed in accordance with the standards of the Department of Health and Human Resources and were approved by the Institutional Animal Care and Use Committee.

Monkeys were randomized by plasma total cholesterol (TC) concentrations at week 12 of the dietary regimen to receive a 6-week infusion of either losartan or vehicle (50% dimethylsulfoxide/50% distilled H₂O, vol/vol) via osmotic minipumps (model 2 ML4, Alza Corp) inserted into the interscapular tissue. Losartan, dissolved in vehicle to a final concentration rate of 1.0 mg/mL, was administered at a rate of 2.5 mg/h. Two weeks after cessation of treatment, monkeys were deeply anesthetized with a mixture of ketamine hydrochloride (40 mg/kg IM) and pentobarbital sodium (50 mg/kg IV). Whole-body perfusion with lactated Ringer’s solution was available at http://www.circulationaha.org

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initiated via a left ventricular cannula at a pressure of 100 mm Hg. The heart was isolated, and coronary arteries were perfused in situ with 10% phosphate-buffered formalin (pH 7.4) for 1 hour. The epicardial segments of the left anterior descending (LAD), circumflex (LCx), and right (RCA) coronary arteries were removed and immersed in 10% phosphate-buffered formalin. Iliac and carotid arteries were placed in the same fixative for determination of TC concentrations. The aorta (from the aortic arch to the iliac bifurcation) was removed, cut open along the longitudinal axis, pinned flat, and immersed in fixative.

**Physiological Studies**

Variables were determined at week 12 of the dietary regimen (baseline), again at weeks 3 and 6 of treatment, and at the end of the recovery period. TriPLICATE measurements of arterial pressure were obtained with an automatic sphygmomanometer in animals lightly anesthetized with ketamine (10 mg/kg IM). Heart rates were calculated from the average number of pulse waves per time.

**Laboratory Procedures**

Samples of venous blood were drawn and, unless noted below, collected into tubes with or without EDTA (Vacutainer, Becton Dickinson) before the regular morning feeding for measurements of plasma lipids, angiotensin peptides, hematological variables, and serum markers.

**Blood Cell Counts**

Automated cell counts were determined in a cell counter (series 9000, Serono Baker Diagnostics) with the cell-size discriminator optimized for this species. Leukocyte differential counts were performed by counting 100 white blood cells on a Wright’s-stained blood smear.

**Monocyte CD11b Assays**

Whole-blood immunophenotyping was performed in 50-μL samples of venous blood diluted in 100 μL of PBS/0.1% BSA by fluorescence-activated cell sorting analysis using mouse-derived monoclonal antibodies to human CD14 (PE-conjugated, clone My4, Beckman Coulter), CD45 (FITC-conjugated, clone 2B11, Dako), and CD11b (FITC-conjugated, clone ICRF44, Pharmingen) receptors. The monocyte acquisition gate was determined by 2-color analysis of fluorescence intensity of cells within the gate established for monocyte acquisition. Monoclonal antibodies were added at room temperature for 20 minutes. Cells were washed once with 1 mL of PBS. Red blood cells were lysed (Whole Blood Lysing Kit, Beckman Coulter), and after 2 additional washings, they were resuspended in 500 μL of PBS/2% paraformaldehyde and refrigerated until analysis. Cell suspensions were analyzed within 24 hours of labeling on an EPICS (Beckman Coulter) flow cytometer using EXPO cytometer software (Beckman Coulter). For each sample, a minimum of 5000 cells were analyzed within the monocyte acquisition gate. Results are reported as the mean fluorescence intensity of cells expressing CD11b.

**Platelet Thrombin Receptor Activation**

Platelet-rich plasma prepared as previously described[13] was incubated at 37°C for 2 minutes and stirred for 1 minute at 1100 rpm in an aggregometer (PAP 4-C, Biodata). The thrombin receptor agonist SFLRRN-NH₂ (5 to 1000 pmol/L) was added at various doses to stimulate platelet aggregation. Results are reported as the concentration of agonist that produced a half-maximal response (C₅₀).

**Circulating Markers**

ELISA kits were used to determine serum concentrations of soluble monocyte chemoattractant protein (MCP)-1 (Cytoscreen Immunassay Kit, Biosource International), vascular cell adhesion molecule (VCAM)-1, and E-selectin (R&D Systems, Inc). Serum C-reactive protein (CRP) concentrations were determined by turbidimetric immunoassay (ALPCO).

**Biochemical Procedures**

**Plasma Cholesterol and Lipoprotein Profiles**

Plasma TC was determined by enzymatic procedures, whereas HDL cholesterol, LDL, VLDL, lipoprotein subclass distributions, and particle sizes were determined by proton NMR spectroscopy.[12] A 360-MHz proton NMR spectrum (Siemens Medical Systems; reconstructed by Analogic) of plasma specimens was obtained at 45°C. Deconvolution of the lipid methyl group signal envelope yielded the derived signal amplitudes broadcast for 14 modeled lipoprotein subclasses. Particle size index (mass-weighted-average size of particles within each lipoprotein class) was calculated by weighting each subclass concentration by a numerical size designation, with large values representing larger particle subclasses.

The susceptibility of LDL to in vitro oxidation was assessed by modification of the technique described by Esterbauer et al.[13] Auto-oxidation was studied at 37°C in quartz cuvettes containing 3 mL of air-saturated 25 mmol/L phosphate buffer, pH 7.2, and 0.1 mol/L NaCl. The solution was mixed with 10 μg/mL LDL protein containing 3.6 μmol/L Cu²⁺ (PolyScience). EDTA and salts were removed by 48 hours of dialysis at 4°C against 25 mmol/L PBS containing 10 μmol/L DTPA with continuous nitrogen sparging. Conjugated diene formation was measured at 236 nm with a diode array spectrometer (model 8452, Hewlett Packard). Concentrations were calculated assuming ε₂36 nm = 26 000 mol/L per cm. The rates of oxidation and lag times were determined as previously described for LDL.[14] Protein was measured with BSA (No. 4503, Sigma-Aldrich) as the standard.[15] The lag phase is the interval between the intercept of the tangent of the slope of the absorbance curve during the diene conjugation phase with the time-scale axis, expressed in minutes. The oxidation rate was calculated from the slope of the absorbance curve during the propagation phase, expressed as pmol diene · min⁻¹ · mg LDL protein⁻¹.

**Plasma Angiotensin Peptides**

Plasma concentrations of Ang II and Ang-(1–7) were determined as described previously.[16] Samples of blood were placed in tubes containing EDTA (25 mmol/L final concentration) and a mixture of protease inhibitors (0.44 mmol/L o-phenanthroline, 0.12 mmol/L pepstatin A, 1 mmol/L 4-chloromercuribenzoic acid) to prevent peptide degradation. After centrifugation at 4°C, the plasma was frozen on dry ice and stored at −20°C until analysis.

**Plasma Losartan and EXP 3174**

Plasma concentrations of losartan and the metabolite EXP 3174 were determined by high-performance liquid chromatography (HPLC) separation/UV detection. The solvent system consisted of 0.1% phosphoric acid (Phos, mobile phase A) and 80% acetonitrile (ACN)/0.1% Phos (mobile phase B). The gradient was 25% B isotropic for 5 minutes, 25% to 50% B linear for 30 minutes, and 50% B isotropic for 10 minutes at a flow rate of 0.35 mL/min at ambient temperature. Analysis was performed on an HPLC (ABI) equipped with a narrow-bore Nova-Pak C₁₈ column (Waters 2.1×150 mm) and an Aquapore C₄ guard column (ABI, 3.2×15 mm). Compounds were monitored at a wavelength of 254 nm (ABI 783 Spectroflow detector), identified by comparison of their retention times with those of standards. Peak areas were determined with a PC Chrom 24-bit data acquisition system (H&S Scientific). The sensitivity of the HPLC analysis was ~10 pmol of losartan. Losartan eluted at 19.9 minutes and EXP 3174 at 29.8 minutes. Before HPLC analysis, plasma samples were extracted and concentrated on Sep-Pak C₁₈ columns (200 mg, Waters). Plasma (2 mL) was acidified with 0.1 Phos, applied to an activated column (5 mL 80% ACN/0.1% Phos, 5 mL 0.1 Phos), and washed with 0.1% Phos and 20% ACN/0.1% Phos. The compounds were eluted in 5 mL 80% ACN/0.1% Phos, and the eluate was completely evaporated in a Savant vacuum centrifuge.
Fatty-Streak Measurements

Aortas were stained by immersion for 24 hours in Sudan IV (in 38% isopropanol, optical density 0.220). Luminal surfaces were digitally imaged by scanning (ScanJet 6200C, Hewlett Packard), and the percentage of fatty-streak surface area was determined by digitizing color images. The histological characteristics of fatty streaks were confirmed by immunological detection.

Fifteen consecutive segments of the LAD, LCx, and RCA (∼5 mm in length) were embedded in paraffin, cut, mounted on glass slides, and stained with Verhoeff–Von Gieson stain. Measurements of the intima thickness and media cross-sectional areas were determined with an imaging system (MCID, Imaging Research, Inc). The intima area was determined by digitizing the area between the internal elastic lamina (IEL) and the luminal surface of each coronary artery. Media area size was calculated by use of the area within the external elastic lamina and IEL.

Monoclonal antibodies to monocyte-macrophages (HAM-56, Boehringer Mannheim) and smooth muscle cells (α-actin, Dako) delineated cell types within vascular cross sections. The immunoperoxidase-avidin-biotin complex system with nickel chloride (NiCl) color modification was used on formalin-fixed paraffin-embedded sections. Five-micrometer sections were deparaffinized, rehydrated with PBS. Sections were preincubated with 3% hydrogen peroxide and 1.0 mL of 8% NiCl solution were added for 10 minutes. Sections were counterstained with hematoxylin, dehydrated in graded series of alcohol concentrations, and covered with coverslips.

The carotid arteries were subjected to Folch extraction and detergent enzymatic digestion for determination of TC (Cholesterol/HP Kit, Boehringer-Mannheim) and free cholesterol (Free Cholesterol C Kit, Wako). Protein was determined as described.18

Statistics

ANOVA was used to determine within-group and between-group differences at baseline, treatment, and recovery. The paired Student’s t test was used where only baseline and treatment values are reported. Square-root transformation of the intimal area in coronary arteries was used to normalize the data before analysis. All tests were 2-tailed, and probability values of <0.05 were considered significant.

Results

Studies were completed in 14 of 20 animals; 8 were randomized to vehicle treatment and 6 to losartan treatment. Experiments were interrupted in 4 animals because of aversion to the diet. Two additional animals were excluded from study because their plasma TC concentrations fell outside the 95% CI at week 12 of the dietary regimen.

Body weights in the vehicle (5.03±0.10 kg) and losartan (5.10±0.15 kg) groups were not different (P>0.05) at baseline and during the treatment and recovery periods (Figure 1). Plasma TC concentrations at week 12 of the dietary regimen averaged 8.12±1.03 and 8.04±0.78 mmol/L in animals randomized to vehicle or losartan treatment, respectively (P>0.05).

Hemodynamic and angiotensin peptide data are presented in Figure 2. Mean arterial pressures at week 12 of the diet and before randomization to vehicle or losartan treatments were 48±5 and 56±5 mm Hg, respectively (P>0.05). After 6 weeks of treatment, mean arterial pressures were 58±3 and 58±4 mm Hg (P>0.05) in losartan- and vehicle-treated animals, respectively. Although systolic and diastolic pressures were never different between treatment groups, systolic pressure in the losartan group was lower (P<0.05) than baseline values at week 4 of treatment. Cardiac rates were not different between vehicle- and losartan-treated animals throughout the study. Vehicle-treated monkeys had lower heart rates than at baseline at the completion of the treatment period and at week 2 of the recovery period. Plasma Ang II and Ang-(1–7) concentrations were significantly increased in animals given losartan. At weeks 3 and 6 of treatment, plasma levels of losartan averaged 377±67 and 464±82 ng/mL, respectively. EXP 3174, the active metabolite of losartan, was detected in the plasma at week 2 (24±6 ng/mL) but not at week 6 of treatment.

Losartan had no effect on plasma cholesterol concentrations, the size of lipoprotein particles, or their distribution within subclasses (Table). Figure 3 illustrates that the susceptibility of LDL to lipid peroxidation (lag time to diene formation and rate of oxidation) in the presence of CuSO4 was not different at baseline between vehicle- and losartan-treated animals. In contrast, the lag time of the CuSO4-induced LDL oxidation was significantly increased (P<0.05) compared with vehicle-treated monkeys at week 6 of losartan treatment. The rate of oxidation was unaffected by treatment.

Effect of Losartan on Atherosclerosis

Figure 4 shows representative examples of fatty-streak distribution in the aorta of vehicle- and losartan-treated mon-
keys. In vehicle-treated monkeys (Figure 4, a and b), sudanophilic areas encompassed both branching and nonbranching areas of the thoracic aorta, whereas fatty streaks were sparse and more prevalent in branching areas of the abdominal aorta. The extent of sudanophilic areas was markedly less in losartan-treated animals (Figure 4, c and d). Figure 5a shows that the layer of foam cells in aortic lesions consistently stopped at the internal elastic lamina (IEL) and that fatty streaks were composed primarily of lipid-loaded HAM-56–positive macrophages (Figure 5b). The histological features of aortic lesions were comparable between vehicle- and losartan-treated monkeys. In contrast, Figure 6 illustrates the differential effect of losartan treatment on the histological characteristics of fatty streaks in the left anterior descending coronary artery (LAD). Whereas in vehicle-treated animals, intimal foam cell accumulation was associated with IEL disruption (Figure 6a) and a predominance of cells immunopositive for α-actin (Figure 6c), a comparable section from a losartan-treated monkey showed a reduction of fatty streak composed of macrophage-derived foam cells and no disruption of the IEL (Figure 6, b and d).

Losartan had a pronounced effect on the extent of fatty streak (Figure 7). Administration of losartan was associated with significantly ($P<0.05$) less fatty streak in the arch (48%), thoracic (52%), and abdominal (54%) aorta than in vehicle-treated monkeys. The intimal area was less ($P<0.05$) only in the LAD and left circumflex coronary artery (LCx), whereas media area was smaller ($P<0.05$) only in the LAD.

### Plasma Lipoprotein Profile

<table>
<thead>
<tr>
<th>Profile Parameter</th>
<th>Control (n=8)</th>
<th>Losartan (n=6)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
</tr>
<tr>
<td>Concentration, nmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>$0.62 \pm 0.13$</td>
<td>$0.70 \pm 0.16$</td>
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<tr>
<td>LDL</td>
<td>$5.09 \pm 0.85$</td>
<td>$5.46 \pm 0.72$</td>
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<tr>
<td>HDL</td>
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<td>$1.58 \pm 0.10$</td>
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<tr>
<td>Particle size, nm</td>
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<tr>
<td>VLDL</td>
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<tr>
<td>LDL</td>
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<tr>
<td>HDL</td>
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<td>$8.7 \pm 1.0$</td>
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<tr>
<td>Particle size index</td>
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<tr>
<td>VLDL</td>
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</tr>
<tr>
<td>LDL</td>
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<td>$4.32 \pm 0.15$</td>
</tr>
<tr>
<td>HDL</td>
<td>$3.07 \pm 0.22$</td>
<td>$2.81 \pm 0.25$</td>
</tr>
</tbody>
</table>

Lipoprotein concentrations, particle sizes, and particle size indices were derived from proton NMR–generated peaks.
Furthermore, the inhibition of fatty-streak formation by losartan was associated with a comparatively lower ($P < 0.05$) carotid artery content of TC and esterified cholesterol.

**Effect of Losartan on Immune Status and Circulating Markers**

Monocyte cell count was not different between vehicle ($2.32 \pm 0.57 \times 10^6$/mL) and losartan ($3.1 \pm 0.43 \times 10^6$/mL) groups at baseline and remained unaltered during treatment and recovery periods. Baseline, treatment, and recovery values for monocyte and platelet activation along with levels of soluble monocyte chemoattractant protein (MCP)-1, vascular cell adhesion molecule (VCAM)-1, E-selectin, and C-reactive protein (CRP) are shown in Figure 8. Surface expression of CD11b by circulating monocytes was unaffected by vehicle but was significantly ($P < 0.05$) reduced in losartan-treated monkeys both at week 6 of treatment and at the end of the recovery period. Platelet aggregability did not differ between vehicle- and losartan-treated animals. Serum MCP-1 was significantly ($P < 0.05$) reduced at week 6 of losartan treatment, with values returning to pretreatment levels during the recovery period. Baseline concentrations of VCAM-1 and E-selectin were higher in the group randomized to losartan than in vehicle-treated monkeys ($P < 0.05$). The difference persisted during the period of infusion. Within each treatment group, however, VCAM-1 and E-selectin concentrations were not different at baseline and week 6 of the infusion period. Conversely, VCAM-1 and E-selectin concentrations showed a significant increase 2 weeks after discontinuation of the infusion in the group of monkeys given losartan. CRP concentrations were not different in vehicle- and losartan-treated animals throughout the study.

**Discussion**

The data presented here represent the first demonstration of Ang II AT$_1$ receptor–mediated fatty-streak formation in a primate model of human atherosclerosis. Plasma concentrations of losartan achieved by the method of continuous subcutaneous infusion used in this study were within the range reported in

![Figure 4. Representative examples in distribution of sudanophilia within aortas of 4 cholesterol-fed monkeys randomized to either vehicle (a and b) or losartan treatment (c and d).](#)

![Figure 5. Representative histological and immunostained sections of thoracic aorta from a vehicle-treated monkey fed an atherogenic diet. a, Intimal accumulation of hematoxylin-eosin–stained foam cells in aorta. b, HAM-56–positive macrophage foam cell accumulation in hematoxylin-counterstained sections. a, Magnification $\times 100$, bar=0.07 mm; b, magnification $\times 400$, bar=0.01 mm.](#)
human subjects given the standard dose of 50 to 100 mg once daily. The extent of hypercholesterolemia-induced fatty streak in aorta and coronary arteries of losartan-treated monkeys was significantly less than in vehicle-treated monkeys and was associated with comparatively lower carotid artery content of TC and esterified cholesterol. These findings agree with results in rabbits and monkeys chronically treated with ACE inhibitors. In these studies, however, blood pressure and plasma lipid concentrations were reduced by the treatments. The inverse relationship between losartan and atherogenesis found in the present study suggests that AT1 receptor–mediated fatty-streak formation is unrelated to changes in blood pressure or lipid subclass concentrations and distributions, because these variables were unaffected by the treatment. These findings differ from observations in rabbits, in which only the dose of irbesartan that lowered blood pressure inhibited atherosclerosis.

Evidence for antiatherogenic mechanisms related to the pronounced fatty-streak inhibition by losartan include a reduced susceptibility of LDL to in vitro CuSO4-induced oxidation, deactivation of circulating monocytes, and suppression of serum soluble MCP-1 levels. Keidar et al showed that losartan reduced LDL peroxidation and atherosclerosis in apolipoprotein E–deficient mice. Although there is no definitive proof that the resistance of LDL to in vitro oxidation reflects the peroxidation potential in vivo, our findings concur with other studies showing that the susceptibility of LDL for oxidation is related to the severity of atherosclerosis. Because CD11b expression is elevated by hypercholesterolemia, it reflects not only monocyte activation but also the propensity for adhesion to endothelium. The deactivation of monocytes by losartan may thus inhibit one of the cardinal events in atherogenesis. We showed previously that AT1 receptor–mediated fatty-streak formation is unrelated to changes in blood pressure or lipid subclass concentrations and distributions, because these variables were unaffected by the treatment. These findings differ from observations in rabbits, in which only the dose of irbesartan that lowered blood pressure inhibited atherosclerosis.

![Figure 6](http://circ.ahajournals.org/)

**Figure 6.** Sections of most proximal segment of an LAD from vehicle- (a) and losartan-treated (b) monkeys stained with Verhoeff–van Gieson stain. Fatty streak in vehicle-treated monkeys was characterized by deposition of α-actin–positive foam cells in both intima and media (c), associated with disruption of IEL. A reduction of foam cell accumulation with preservation of IEL and absence of α-actin–positive foam cells (d) characterized fatty streak in a losartan-treated monkey. a and b, Magnification ×100, bar=0.07 mm; c and d, corresponding sections from boxed regions of a and b, magnification ×400, bar=0.01 mm.

![Figure 7](http://circ.ahajournals.org/)

**Figure 7.** Extent of dietary hypercholesterolemia-induced fatty-streak lesions determined by percentage of aorta intimal surface areas stained for lipid by Sudan IV, coronary artery intima areas, and cholesterol contents within carotid arteries from monkeys treated for 6 weeks with either vehicle (solid bars) or losartan (open bars). Aorta areas are divided into Arch, thoracic (Thor), and abdominal (Abdo) sections. FC and CE indicate free and esterified cholesterol contents of carotid arteries, respectively. *P<0.05 vs vehicle.
In summary, losartan inhibited the development of fatty streak and reduced media area of coronary arteries by a mechanism that was independent of arterial pressure and plasma lipids. The reduction in the extent of fatty streak was accompanied by decreases in the carotid artery content of TC and esterified cholesterol, measures of LDL peroxidation, and monocyte activation. We conclude that the novel effects of losartan on early atherogenesis may extend the therapeutic profile of Ang II antagonists in the prevention of human vascular disease, an interpretation that agrees with the observation that atherosclerosis is associated with upregulation of AT1 receptors.25

Acknowledgments

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References

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