Suppression of experimental abdominal aortic aneurysms in the rat by treatment with angiotensin-converting enzyme inhibitors

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Purpose: **Pathologic remodeling of the extracellular matrix is a critical mechanism in the development and progression of abdominal aortic aneurysms (AAAs). Although angiotensin-converting enzyme (ACE) inhibitors are known to alter vascular wall remodeling in other conditions, their effects on AAAs are unknown. In this study we assessed the effect of ACE inhibitors in a rodent model of aneurysm development.**

Methods: **Male Wistar rats underwent transient aortic perfusion with porcine pancreatic elastase, followed by treatment with one of three ACE inhibitors (captopril [CP], lisinopril [LP], or enalapril [EP]), an angiotensin $(AT)_1$ receptor antagonist (losartan [LOS]), or water alone (9 rats in each group). Blood pressure and aortic diameter (AD) were measured before elastase perfusion and on day 14, with an AAA defined as an increase in AD (ΔAD) of more than 100%. The structural features of the aortic wall were examined by means of light microscopy.**

Results: **Aneurysmal dilatation consistently developed within 14 days of elastase perfusion in untreated rats, coinciding with the development of a transmural inflammatory response and destruction of the elastic media (mean ΔAD, 223% ± 28%). All three ACE inhibitors prevented AAA development (mean ΔAD: CP, 67% ± 4%; LP, 18% ± 12%; and EP, 14% ± 3%; each $P < .05$ vs controls). ACE inhibitors also attenuated the degradation of medial elastin without diminishing the inflammatory response. Surprisingly, the aneurysm-suppressing effects of ACE inhibitors were dissociated from their effects on systemic hemodynamics, and LOS had no significant effect on aneurysm development compared with untreated controls (mean ΔAD, 186% ± 19%).**

Conclusion: **Treatment with ACE inhibitors suppresses the development of elastase-induced AAAs in the rat. Although this is associated with the preservation of medial elastin, the mechanisms underlying these effects appear to be distinct from hemodynamic alterations alone or events mediated solely by AT_1 receptors. Further studies are needed to elucidate how ACE inhibitors influence aortic wall matrix remodeling during aneurysmal degeneration. (J Vasc Surg 2001;33:1057-64.)**

Abdominal aortic aneurysms (AAAs) are characterized by segmental dilatation of the aortic wall and pathologic remodeling of the extracellular matrix.[1] Although elastin and collagen normally provide the resilience and tensile strength needed for the aorta to withstand hemodynamic stress, destruction of the elastic media is an early event in aneurysmal degeneration, and collagen degradation is considered necessary for aneurysm expansion and rupture.[2] Human and experimental AAAs are also associated with chronic transmural inflammation and elevated local expression of enzymes that mediate matrix protein degradation, including matrix metalloproteinases (MMPs), plasminogen activators, and cathepsins.[3-7] Pharmacologic strategies aimed at preventing matrix degradation may therefore have promise in the management of small asymptomatic AAAs.[8]

Angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of hypertension, congestive heart failure, and other cardiovascular disorders.[9,10] In addition to their antihypertensive effects, these compounds are recognized as having a substantial influence on connective tissue remodeling after myocardial infarction or vascular wall injury.[11,12] In many circumstances, these effects arise through a direct modification of fibroproliferative tis-

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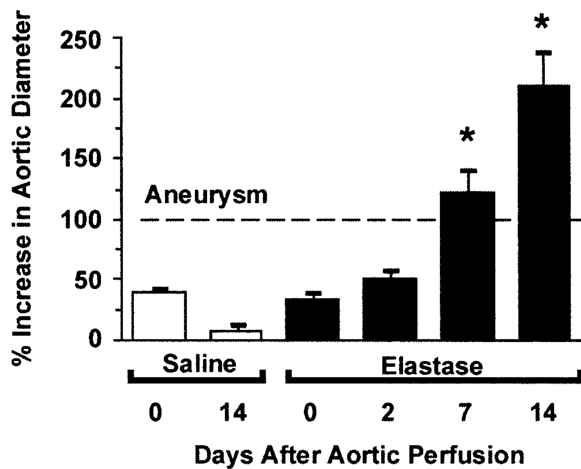

Fig 1. Development of elastase-induced abdominal aortic aneurysms in the rat. AD measurements after transient perfusion with either saline or elastase are expressed as percent increase between preperfusion and final AD. Each *bar* represents mean ± SEM for six rats. AAAs (*horizontal line*) consistently developed within 7 days of elastase perfusion and were uniformly present by day 14. **P* < .05 vs day 0, Student *t* test.

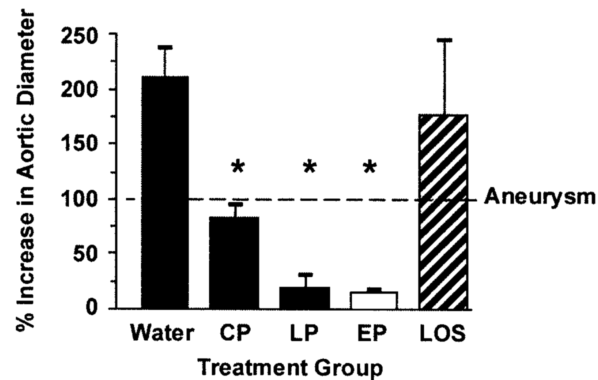

Fig 2. Effect of ACE inhibitors on the development of elastase-induced AAAs. Aneurysmal dilatation was assessed 14 days after elastase perfusion in animals treated with water alone or water supplemented with 250 mg/L of either captopril (*CP*), lisinopril (*LP*), enalapril (*EP*), or losartan (*LOS*). Each *bar* represents mean ± SEM for six rats, with AAAs (*horizontal line*). **P* < .05, compared with water-treated controls.

sue healing rather than hemodynamic changes alone, and they may involve inhibition of ACE in the vessel wall, as opposed to the circulating enzyme alone.[13-15] ACE inhibitors prevent the generation of angiotensin-II (Ang-II), and many of the effects of Ang-II involve activation of cellular AT_1 receptors; thus, specific AT_1 receptor antagonists have also been developed for clinical application.[16,17] Despite the widespread use of ACE inhibitors and AT_1 receptor antagonists in patients with cardiovascular disease, their potential effects on aortic aneurysms are unknown.

In this study we investigated whether treatment with ACE inhibitors has a favorable influence on the process of aneurysmal degeneration. To test this, we examined the effects of three different ACE inhibitors and a selective AT_1 receptor antagonist on the development of elastase-induced AAAs in the rat. Our results demonstrate that ACE inhibitors consistently suppress experimental aortic aneurysms by attenuating aortic wall connective tissue destruction, but that these effects are distinct from changes in systemic hemodynamics alone or events mediated solely by AT_1 receptors. These findings provide a basis for further investigations on the molecular mechanisms of aneurysmal degeneration and suggest the potential usefulness of ACE inhibitors in patients with AAAs.

MATERIALS AND METHODS

Elastase perfusion model of abdominal aortic aneurysm. Male Wistar rats (350-400 g) underwent transient perfusion of the abdominal aorta according to a protocol approved by the Washington University Animal Care Committee, as described.[18-20] In brief, a laparotomy was performed under sterile conditions, and the abdominal aorta was exposed from the level of the left renal vein to the aortic bifurcation. A PE-10 polyethylene catheter (Baxter, McGraw Park, Ill) was introduced through a femoral arteriotomy, and its tip was positioned within the distal abdominal aorta. The preperfusion aortic diameter (AD) was measured to within 0.05 mm with a binocular surgical microscope equipped with a scaled grid (Leica, Deerfield, Ill). The infrarenal aorta was clamped above the level of the catheter tip, and a silk ligature was secured around the aortic bifurcation to encompass the catheter without occluding it. The isolated segment of distal abdominal aorta (approximately 15 mm in length) was then perfused with 2 mL of saline alone or saline containing 50 units of type I porcine pancreatic elastase (E-1250 purchased before February 1997, Sigma Chemical, St Louis, Mo).[21] Aortic perfusion was performed in a 2-hour period with a syringe pump to maintain pressure at 100 mm Hg (Sage Instruments, Boston, Mass). After perfusion, the aortic clamp and silk ligatures were removed, the polyethylene catheter was withdrawn, and the femoral artery was ligated. The postperfusion AD was measured 5 minutes after restoration of the aortic blood flow. Animals were allowed to recover from anesthesia and were maintained in individual cages with free access to food and water for as long as 14 days. At that time, the abdominal aorta was reexposed through a laparotomy, and the final AD was remeasured under physiologic conditions immediately before the rats were euthanized with intravenous pentobarbital. Measurements of the preperfusion, postperfusion, and final AD were recorded for each animal. The increase in AD was calculated (ΔAD = final AD – preperfusion AD) and expressed as a percentage change for each animal (ΔAD%). An AAA was defined as a ΔAD% greater than 100.

Control groups. Two control groups were used to verify the consistency of aneurysm development. The first group consisted of six rats that underwent aortic perfu-

Table I. AD measurements in drug treatment groups

Treatment	*AD Pre (mm)*	*AD Post (mm)*	*AD Final (mm)*	*ΔAD (mm)*	*No. of AAAs*
Water	1.60 ± 0.02	2.78 ± 0.07	5.17 ± 0.44	3.57 ± 0.75	6 of 6
Captopril	1.61 ± 0.03	2.41 ± 0.06	2.96 ± 0.21*	1.34 ± 0.34*	0 of 6†
Lisinopril	2.08 ± 0.03	2.51 ± 0.05	2.47 ± 0.26*	0.39 ± 0.25*	0 of 6†
Enalapril	1.99 ± 0.08	2.45 ± 0.08	2.34 ± 0.15	0.35 ± 0.09*	0 of 6†
Losartan	1.65 ± 0.02	2.45 ± 0.08	4.58 ± 0.57	2.92 ± 0.80	6 of 6

Measurements were obtained immediately before (*Pre*) and after (*Post*) elastase perfusion and 14 days later (*Final*). The increase in AD (Δ*AD*) was determined for each animal to be the difference between final AD and the preelastase baseline AD. The number of individual animals in which AAAs developed (ΔAD > 100%) was recorded. Animals were treated with the agents indicated beginning on the day of elastase perfusion (250 mg/L in the drinking water). All data represent the mean ± SEM.
*$P < .05$ vs water, Student *t* test.
†$P < .05$ vs water, χ^2 analysis.

sion with saline alone, then were killed on day 14. The second group consisted of 18 rats that underwent aortic perfusion with elastase, then were killed on day 2, 7, or 14 (6 rats at each interval). All control animals were provided with free access to normal drinking water for the entire period after perfusion.

Experimental (pharmacologic treatment) groups. There were four experimental groups, each consisting of nine rats that underwent aortic perfusion with elastase. Beginning on the day of elastase perfusion, experimental animals were given drinking water supplemented with 250 mg/L of captopril (CP), lisinopril (LP), enalapril (EP), or losartan (LOS). A generic form of CP was purchased from Sigma Chemical, and proprietary forms of LP (Prinivil), EP (Vasotec), and LOS (Cozaar) were purchased from Merck (West Point, Pa). The route of administration that was used resulted in a daily intake of 4 to 6 mg/kg for each compound tested, a dose consistent with other experimental studies in rats in which these agents have exerted significant pharmacologic effects.[22-25]

Hemodynamic measurements. Three rats in each group were used as a means of determining the effect of drug treatment on systemic hemodynamics. At the time of transfemoral cannulation of the abdominal aorta, arterial blood pressure (BP) and ambient heart rate were measured directly and recorded on a strip-chart (Gould Instrument Systems, Valley View, Ohio). Six individual recordings were made in a 30-minute period of stabilization, and the mean (± SE) of these values was used to establish the pretreatment baseline conditions for each animal. Hemodynamic measurements were repeated with the same technique after 14 days of drug treatment (or water alone).

Histology. After euthanasia, three animals in each group underwent systemic perfusion with 10% neutral buffered formalin (120 mm Hg for 10 minutes). The involved segment of abdominal aorta was excised, immersed in 10% neutral buffered formalin (4°C overnight), and processed for routine paraffin embedding. Aortic tissue cross sections (7 µm) were stained with Verhoeff-van Gieson stain for elastin and examined under a BX60 light microscope with a PM-30 automatic photomicrographic system (Olympus America, Melville, NY).

Statistical analysis. For each of the control and drug treatment groups, the mean ± SE of preperfusion AD, postperfusion AD, final AD, ΔADmm, and ΔAD% was determined, along with the percent of animals that had AAAs. Statistical comparisons between the groups were made with analysis of variance (ANOVA) with the Student-Newman-Keuls multiple comparisons test; the 2-tailed, unpaired Student *t* test; or χ^2 analysis.[26] The overall percent inhibition of aortic dilatation for each drug was determined by comparing the mean ΔAD% for each treatment group with that of the elastase perfused, untreated control group. For analysis of hemodynamic data, the differences between pretreatment and posttreatment BP measurements were compared for each group of rats with the paired Student *t* test. Pearson correlation coefficients were used to determine whether there was any relationship between the effects of drug treatment on aneurysmal dilatation and the effects on systolic, diastolic, or mean BP.

RESULTS

AD consistently increased by approximately 30% immediately after aortic perfusion with either saline or elastase, but subsequently decreased to normal in animals perfused with saline alone (Fig 1). In contrast, AD was stable for as long as 2 days in animals undergoing perfusion with elastase, followed by a progressive increase. The mean AD thus reached aneurysmal proportions in most elastase-perfused animals by day 7 and enlarged further by day 14, with AAAs developing in all animals by this interval. These findings are consistent with our earlier studies on the temporal development of elastase-induced AAAs in the rat.[18-20,27]

Table I summarizes the effects of drug treatment on AD measurements after elastase perfusion. Although aneurysmal dilatation developed in all animals given normal drinking water by day 14, treatment with ACE inhibitors resulted in a significant reduction in both final AD and ΔAD. This inhibitory effect was greatest for EP and LP, but it was also significant for CP; indeed, no AAAs were observed in any of the rats treated with ACE inhibitors ($P < .05$). These experiments also revealed that treatment with the AT_1 receptor antagonist, LOS, had no significant effect on either final AD or ΔAD, with all of the

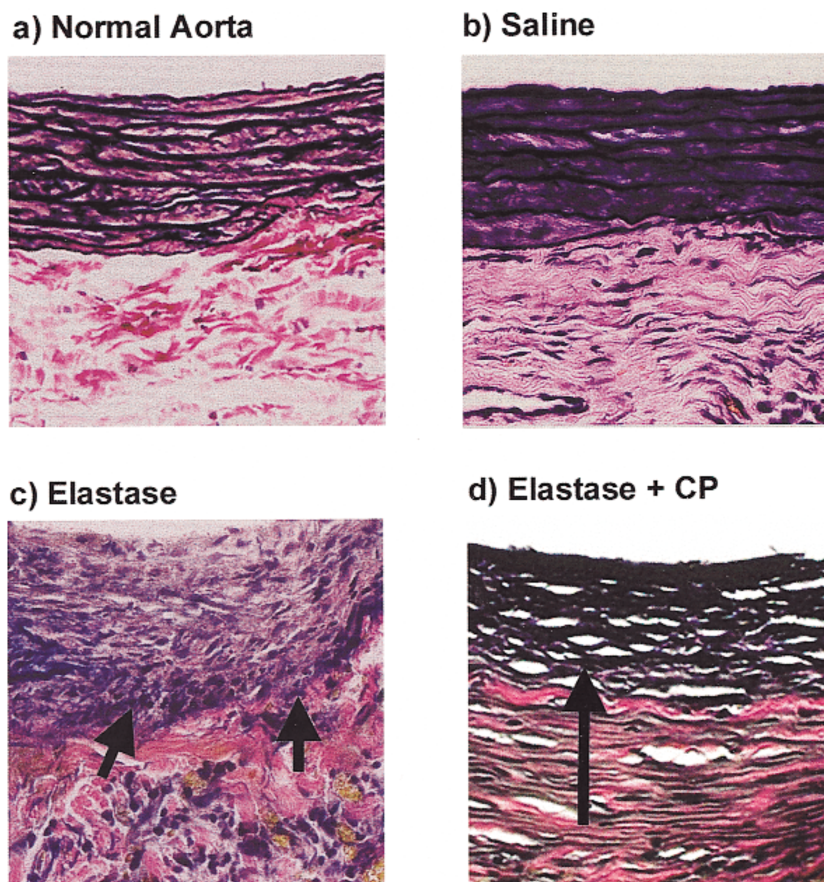

Fig 3. Effect of ACE inhibitors on histology of elastase-induced AAAs. Transverse sections of formalin-fixed aortic tissue were stained with Verhoeff-van Gieson stain for elastin. **a,** Normal preperfusion aorta. **b,** Fourteen days after perfusion with saline, no aneurysmal dilatation. **c,** Fourteen days after perfusion with elastase, marked aneurysmal dilatation. **d,** Fourteen days after perfusion with elastase and captopril (*CP*) treatment, no aneurysmal dilatation. Elastase-induced AAAs were associated with chronic inflammation and destruction of medial elastin (*short arrows*). Treatment with ACE inhibitors was associated with preservation of elastic lamellae (*long arrow*; original magnification, 100×).

LOS-treated animals exhibiting AAAs on day 14. As illustrated in Fig 2, similar results were observed for the extent of aortic dilatation in each of the treatment groups. Compared with that of untreated controls, the overall inhibition of aortic dilatation was 70% for CP, 92% for LP, and 94% for EP.

Fig 3 illustrates the characteristic histopathologic changes that occurred during the development of elastase-induced AAAs. Compared with the normal (preperfusion) aorta, there was little alteration in medial elastin 14 days after perfusion with saline. In contrast, 14 days after perfusion with elastase and treatment with normal drinking water, aneurysmal dilatation was associated with a chronic transmural inflammatory response and extensive destruction of the medial elastic lamellae. This is consistent with our earlier observations in this model, in which aneurysmal dilatation is closely associated with a mononuclear inflammatory response and widespread degradation of medial elastin.[18-20,27] Most important, we found that animals undergoing elastase perfusion and treatment with ACE inhibitors exhibited obvious preservation of aortic wall elastin. This occurred with each of the three ACE inhibitors tested, and it did not appear to be associated with a reduction in the aortic wall inflammatory response.

Changes in systemic BP were measured before and after 14 days of drug treatment to evaluate whether there was any correlation between the aneurysm-suppressing effects of ACE inhibitors and their hemodynamic effects (Table II). The mean BP in water-treated rats was unchanged between the two time points, and the SE of these measurements was less than 5% of the recorded values. In addition, these BP measurements were similar to those obtained in other studies with normotensive Wistar rats by means of either direct catheterization or tail-cuff plethysmography.[28] There were considerable differences in the hemodynamic effects of the compounds used in this study at the single dose tested, with LP producing the greatest effect on mean BP (38% reduction) and EP

Table II. BP measurements in drug treatment groups

	Water	*Captopril*	*Lisinopril*	*Enalapril*	*Losartan*
Systolic BP (mm Hg)					
Day 0	118 ± 3	117 ± 2	131 ± 2	133 ± 3	123 ± 2
Day 14	128 ± 4	107 ± 2	88 ± 4	128 ± 5	131 ± 4
Δ	(+7.3%)	(–8.6%)*	(–33.1%)	(–4.0%)	(+6.1%)
Diastolic BP (mm Hg)					
Day 0	91 ± 1	92 ± 1	105 ± 1	104 ± 2	92 ± 1
Day 14	89 ± 2	78 ± 2	62 ± 4	93 ± 3	91 ± 3
Δ	(–2.0%)	(–15.8%)*	(–41.4%)*	(–10.6%)	(–0.8%)
Mean BP (mm Hg)					
Day 0	100 ± 2	100 ± 2	114 ± 1	114 ± 2	103 ± 1
Day 14	102 ± 3	87 ± 2	70 ± 4	105 ± 5	105 ± 3
Δ	(+1.7%)	(–13.1%)*	(–38.2%)*	(–8.0%)	(+2.0%)

Aortic BP measurements were obtained in a 30-minute period through a transfemoral catheter on day 0. Animals were treated for 14 days with either water alone or the indicated drugs (250 mg/L in the drinking water), and the BP measurements were repeated. The change in BP (Δ) was determined for each animal to be the difference between the final and the pretreatment baseline. All data represent the mean ± SEM.
*$P < .05$ vs water, Student t test.

the least (8% reduction). Treatment with LOS was also associated with no significant hemodynamic changes (2% increase in mean BP). Fig 4 illustrates the disparity between the hemodynamic actions of these drugs and their effects on aneurysm development. Although LP and EP both resulted in a pronounced suppression of aortic dilatation, their effects on BP differed widely. Furthermore, there was no discernible difference between the hemodynamic effects of EP and LOS, but the effects of these two agents diverged markedly for aneurysmal dilatation. We therefore found no significant relationship between the suppressive effects of ACE inhibitors on aneurysmal dilatation and their potential effects on hemodynamic wall stress.

DISCUSSION

The purpose of this study was to begin investigating the potential effects of ACE inhibitors on the development of aortic aneurysms. This is important because AAAs are a common life-threatening disease for which no pharmacologic treatment yet exists and because ACE inhibitors are widely used in the management of cardiovascular disorders that often occur in conjunction with AAAs. Effects of ACE inhibitors on the remodeling of cardiovascular tissues may also have implications for the pathophysiologic mechanisms of aneurysm disease. By using an elastase-induced rodent model, we found that treatment with each of three different ACE inhibitors effectively prevented the development of aneurysms in vivo. Although these ACE inhibitors did not appear to alter the influx of mononuclear inflammatory cells into the elastase-injured aortic wall, their inhibitory effects on aortic dilatation were associated with the preservation of aortic medial elastin, a finding consistent with the notion that matrix degradation is critical in aneurysm development. The results of this study thereby demonstrate for the first time that treatment with ACE inhibitors can suppress the development of experimental AAAs.

Earlier studies have demonstrated that chronic transmural inflammation and elevated expression of MMPs make essential contributions to the development of elastase-induced aneurysms in the rat.[29,30] The response to elastase perfusion includes delayed aortic wall infiltration by mononuclear phagocytes, which is temporally associated with elastin degradation and elevated local production of elastolytic MMPs.[18,30] Elastase-induced aneurysmal dilatation is attenuated by treatment with glucocorticoids, immunosuppressant agents, and leukocyte-depleting monoclonal antibodies, all of which interfere with the chronic inflammatory response.[31,32] Elastase-induced aneurysms are also suppressed by nonsteroidal anti-inflammatory drugs, MMP-inhibiting tetracycline derivatives, and other direct MMP inhibitors; in each case, the effect on aortic dilatation coincides with structural preservation of aortic medial elastin without an alteration in the inflammatory response.[18-20,33-35] These experimental observations suggest that anti-inflammatory drugs or pharmacologic suppression of matrix-degrading enzymes might eventually be useful means of preventing aneurysm expansion in patients with small, asymptomatic AAAs.[8,36-38] The current study indicates that treatment with ACE inhibitors should also be considered among the potential pharmacologic strategies for aneurysm disease.

Our findings demonstrated no correlation between the hemodynamic effects of ACE inhibitors and their suppression of AAAs, leading us to conclude that the aneurysm-suppressing effects of ACE inhibitors cannot be explained solely by changes in systemic hemodynamics. Normotensive adult rats were used in the current study, and we obtained direct BP measurements with an intraarterial catheter under similar experimental conditions at each time point. The reliability and reproducibility of these measurements are indicated by the observation that BP in water-treated rats was unchanged between the two time points, and that in each case, the SE was less than 5% of the mean recorded values. The BP measurements

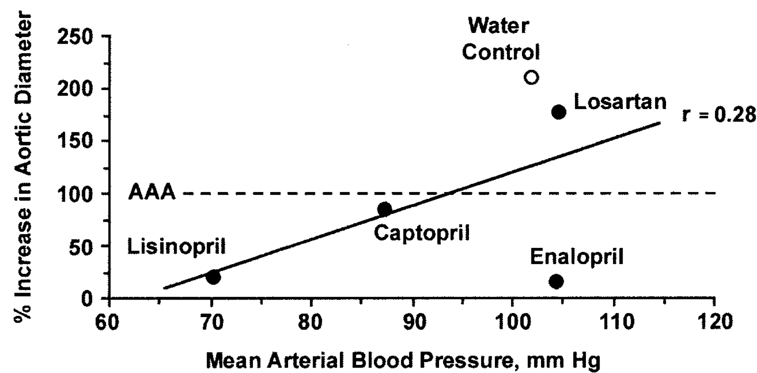

Fig 4. Comparison of ACE inhibitors, aortic dilatation versus hemodynamic effects. Effects of different agents on elastase-induced aortic dilatation at day 14 are compared with their effects on mean arterial BP, with abdominal aortic aneurysms (*AAAs*) indicated *(horizontal line*). There was no significant correlation demonstrated, $r = 0.28$), indicating that ACE inhibitors suppress aneurysmal degeneration by a mechanism(s) independent of their hemodynamic effects.

obtained in control animals also were similar to those in other studies with normotensive male Wistar rats with either direct catheterization or tail-cuff plethysmography.[28] Other studies in which the elastase-induced rat model was used support the view that a reduction in systemic BP is insufficient to suppress AAAs. For example, Slaiby et al[39] found that beta-adrenergic blockade with propranolol did not affect aneurysmal dilatation in normotensive rats, although it did suppress the accelerated aneurysm development observed in rats with spontaneous hypertension. Because we compared each of the drugs used in the current study at a single dose, it remains possible that more pronounced effects on AAAs might have been observed at doses resulting in more substantial hemodynamic changes, at least for some of the compounds tested (including LOS). Further studies will therefore be needed to examine the dose-specific effects of these agents on aneurysm development and to examine how our results might have been altered in the presence of sustained hypotension. It will also be of interest to examine the effects of ACE inhibitors and AT_1 receptor antagonists on elastase-induced AAAs in hypertensive rats.

Because ACE inhibitors act to prevent the conversion of Ang-I to Ang-II, the results of this study suggest that Ang-II plays an important role in the pathophysiology of aneurysmal degeneration. This notion is also supported by two recent experimental studies in genetically altered mice. For example, Nishijo et al[40] found that transgenic overexpression of Ang-II is associated with the development of aneurysmal aortic lesions in hypertensive animals placed on a high-salt diet. These lesions had histologic features of aortic dissection and they were frequently complicated by rupture, but there was no association between the occurrence of these lesions and further alterations in the hypertension exhibited by these animals. More recently, Daugherty et al[41] found that sustained infusion of Ang-II leads to aneurysmal lesions in the atherosclerosis-prone *apoE*$^{-/-}$ mouse and that this occurs in the absence of systemic hypertension. The aortic lesions included chronic inflammation in the outer aortic wall and breaks in the elastic media, but were not associated with atherosclerotic plaques, thereby bearing similarity to the type of aneurysmal degeneration that occurs in the elastase perfusion model. Because aneurysms were not observed in apoE-deficient mice in the absence of Ang-II infusion, the authors concluded that the combination of hyperlipidemia and Ang-II had accelerated the development of aortic wall inflammation. This is consistent with evidence that Ang-II has a direct effect on monocyte recruitment and macrophage activation,[42-46] supporting the view that Ang-II might directly contribute to the development of aneurysmal dilatation.

ACE and Ang-II are recognized as having important effects on vessel wall remodeling and on the functional behavior of vascular wall cell types, including smooth muscle cells and mononuclear phagocytes.[42-48] Ang-II acts to stimulate smooth muscle cell proliferation, matrix deposition, and expression of plasminogen activator inhibitor-1 (PAI-1),[49-54] and its effects on target cells occur through several different receptors. Because in many situations the effects on fibrotic tissue remodeling appear to be mediated by the AT_1 receptor subtype,[55] the effects of ACE inhibitors can often be reproduced by specific AT_1 receptor antagonists. To further investigate the possibility that ACE inhibitors might have mediated the suppression of AAAs through a reduction in Ang-II, we examined the effects of the AT_1 receptor antagonist, LOS. This compound had no significant effect on either aortic elastin degradation or aneurysm development, indicating that the effect of ACE inhibitors in the elastase-induced rat model cannot be explained solely by a reduction in AT_1 receptor-mediated events. These observations, however, do not exclude the possibility that ACE inhibitors might have suppressed activities mediated by other Ang-II receptor subtypes,[56-60] that they may have influenced local production of other biologically active angiotensins (eg, Ang-III

and Ang-IV),[61,62] or that they may have exerted their effects by inhibiting the degradation of vasoactive kinins.[12] Further investigations will be required to determine whether these additional pharmacologic effects of ACE inhibitors are responsible for modulating connective tissue destruction in the aneurysmal aorta.

Another mechanism that may explain the effects of ACE inhibitors in this study resides in the capacity of these compounds to directly block the activity of MMPs. Like converting enzyme, all members of the MMP family are zinc-dependent metalloenzymes. Recent studies indicate that the proteinase-inhibiting effects of at least some ACE inhibitors can also extend to MMPs and that these effects can be sufficient to inhibit MMP-mediated processes such as tumor growth and metastasis, angiogenesis, and experimental heart failure.[63-66] It is therefore quite possible that ACE inhibitors might have acted to inhibit elastin-degrading members of the MMP family that play a crucial role in aneurysmal degeneration, such as gelatinase B (MMP-9).[67] This hypothesis is supported by our observation that aortic elastin was well preserved in elastase-perfused animals treated with ACE inhibitors, despite the presence of mononuclear inflammation. Further studies will be required, however, to elucidate whether the suppression of aneurysmal dilatation by ACE inhibitors is caused by a direct pharmacologic inhibition of elastin-degrading MMP activities within the elastase-injured aortic wall. The recent development of a murine model of elastase-induced AAAs may facilitate efforts to address this question with more specificity, with genetically altered mice.[67]

In conclusion, this study demonstrated for the first time that ACE inhibitors have an important influence on experimental aneurysmal degeneration. It is not yet clear how these compounds achieve this effect, and additional investigations will be needed to elucidate the molecular, cellular, and physiologic mechanisms in more detail. It is also not known whether these experimental observations can be extended to aneurysmal degeneration as it occurs in humans, because there is no information yet available on how ACE inhibitors influence aneurysm expansion in patients with small asymptomatic AAAs. It will, therefore, be of interest to examine these questions in future investigations.

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