Chronic ACE Inhibition Reduces Intimal Hyperplasia in Experimental Vein Grafts

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Intimal hyperplasia is an important factor in the pathophysiology of vein graft failure. Local renin-angiotensin systems recently have been shown to modulate the development of intimal hyperplasia in arteries after intimal injury. The effect of chronic angiotensin-converting enzyme (*ACE*) inhibition on the development of intimal hyperplasia in experimental vein grafts was examined in this study. Ten New Zealand White rabbits received 10 mg/kg of captopril daily in their drinking water. One week later the right carotid artery was divided and bypassed with the reversed right external jugular vein in these rabbits and in 10 matched controls. Captopril was continued for 28 days after operation, when all the grafts were harvested. Five grafts from each group were perfusion fixed, and the intimal thickness in the proximal, middle, and distal segments was determined. Rings from the remaining grafts (n = 20 in each group) were studied *in vitro* under isometric tension, and their responses to norepinephrine (NE), histamine (HIST), serotonin (5-HT), angiotensin I (AI), and angiotensin II (AII) was measured. The intimal thickness of the proximal, middle, and distal segments of the captopril-treated grafts were significantly less than controls, being reduced in all segments by approximately 40% ($p < 0.0001$). With regard to vasoreactivity, the captopril-treated grafts were hypersensitive to 5-HT (control ED_{50} $5.5 \pm 0.5 \times 10^{-7}$ mol/L *vs.* captopril-treated $1.1 \pm 0.2 \times 10^{-6}$ mol/L; $p < 0.005$) although the maximal response was significantly reduced (control 1.6 ± 0.3 g *vs.* captopril-treated 0.8 ± 0.1 g; $p < 0.05$). There were no differences in sensitivity between control and captopril-treated rings with respect to NE, HIST, AI, or AII. Four of the ten captopril-treated segments, however, failed to respond to AI, and the maximal active tension of the responders was significantly reduced (control 0.47 ± 0.06 g *vs.* 0.20 ± 0.05 g; $p < 0.02$). These results suggest that ACE is involved in the modulation of vein graft intimal hyperplasia, and that ACE inhibitors may have therapeutic applications in patients undergoing vein bypass procedures.

Presented at the Forum for Fundamental Problems in Surgery, American College of Surgeons Annual Clinical Congress, San Francisco, California, October 1990.

Supported by U.S. Public Health Service Grants Nos. HL 15448, HL32720, and HL08086.

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Accepted for publication May 22, 1991.

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AUTOGENOUS SAPHENOUS VEIN is the preferred conduit for most arterial bypass procedures where the vessel sizes are compatible and no suitable arterial graft is available. Vein graft failure, however, remains a significant clinical problem.[1-3] The pathophysiology of vein graft failure has not been clearly elucidated. Autogenous vein grafts undergo structural and functional alterations after exposure to the arterial circulation. Intimal thickening develops in all veins within a short period after grafting. The pathologic significance of intimal thickening is uncertain, although some authors suggest that it may be a precursor to the development of atheroma and ultimate graft failure.[4-6] Localized regions of intimal hyperplasia have been associated with graft stenoses and may be harbingers of graft occlusion.[7]

The role of the renin-angiotensin system in the pathogenesis of atherosclerosis is unclear. There is, however, convincing evidence that local renin-angiotensin systems exist in many arteries and veins.[8,9] The activity of these systems results in the local production of angiotensin II independent of the systemic renin-angiotensin system. Angiotensin-converting enzyme (ACE) is a membrane-bound enzyme present in the endothelium of many large and medium-sized vessels in the peripheral circulation. It converts the relatively inactive angiotensin I (AI) to the potent vasoconstrictor angiotensin II (AII). The smooth muscle cells of these vessels have numerous AII receptors. AII has been shown to stimulate hypertrophy in cultured smooth muscle cells and to induce production of the proto-oncogenes c-*fos* and c-*myc*, as well as in the A chain of platelet-derived growth factor (PDGF).[10-12]

Local renin-angiotensin systems may be involved in

the response of blood vessels to intimal injury occurring after angioplasty, endarterectomy, and vein grafting. Inhibition of ACE has been shown to significantly reduce intimal hyperplasia after balloon-catheter injury in rat carotid artery and to have antiatherogenic effects in heritable hyperlipidemic rabbits and cholesterol-fed monkeys.[13–15] The aims of the present study were to examine the effect of chronic *ACE* inhibition on the development of intimal hyperplasia and the vasomotor function of experimental vein grafts.

Materials and Methods

Experimental Design

Two groups of age and weight-matched adult male New Zealand White rabbits weighing 2 to 2.5 kg were studied. In 10 animals, captopril was administered in a dose of 10 mg/kg/day in the animals' drinking water; 10 additional animals were used as controls. One week later all animals underwent reversed autogenous vein bypass grafting of the right common carotid artery using the right external jugular vein. Blood pressure was measured at intervals during the study and the grafts were harvested after 28 days. Five grafts in each group were perfusion fixed for examination by light microscopy and the remainder studied *in vitro* under isometric tension. The grafts' responses to norepinephrine (NE), histamine (HIST), angiotensin I (AI), angiotensin II (AII), and serotonin (5-HT) were assessed. The animals received a normal diet during the period of study. Animal care complied with the "Principles of Laboratory Animal Care" and the "Guide for the Care and Use of Laboratory Animals" (NIH Publication No. 80-23, revised 1985).

Animal Operations

General anesthesia was induced and maintained for all operations using ketamine (60 mg/kg), acepromazine (1 mg/kg), and xylazine (5 mg/kg) intramuscularly. A single dose of prophylactic antibiotic in the form of 30,000 IU/kg of benzanthine and procaine penicillin (Durapen; Vedco, Inc., Overland Park, KS) was given intramuscularly at the time of induction. The right external jugular vein was harvested through a longitudinal neck incision as previously described.[16] The vein was stored in heparinized saline (5 IU/ml) while the common carotid artery was mobilized. The rabbit then was systemically heparinized (200 IU/kg IV), and a 4-cm section of the common carotid artery isolated between clamps. The vein was reversed and an end-to-side anastomosis was created with continuous 10–0 monofilament nylon suture (Ethicon, Inc., Somerville, NJ). The artery was ligated and divided between the anastomoses, leaving a graft of approximately 3 cm in length.

Four weeks later the animals were reanesthetized as described previously. The vein grafts from five animals in each group were left *in situ* and, after death, were fixed by perfusion and processed for histology. The vein grafts for *in vitro* study were removed atraumatically through longitudinal incisions and placed in oxygenated Krebs solution. Four rings, 4 to 5 mm in length, were cut from the central portion of each graft in preparation for isometric tension studies.

Blood Pressure Measurement

The arterial pressure of all animals was measured through a cannula placed in the middle ear artery using a catheter-tipped pressure transducer (Millar Instruments Inc., Houston, TX). Measurements were obtained before entry into the study, at the time of vein grafting, and at the time of harvest. Blood pressure was continuously monitored with the animal awake in a quiet environment and the pressure recorded when stable.

Histology

The grafts chosen randomly for histology were exposed under general anesthesia. The animal was systemically heparinized (500 IU/kg) and killed with an overdose of sodium pentobarbital. The thoracic aorta was exposed and cannulated and the graft perfused at the animal's last recorded blood pressure with normal saline followed by 10% formaldehyde. After 30 minutes' fixation *in situ,* the grafts were removed, fixed overnight by immersion, and divided into proximal, middle, and distal segments. The segments were paraffin sectioned at 5 μm and stained with modified Masson's trichrome and Verhoeff's elastic tissue stains.[17] The sections were examined by light microscopy in a blinded fashion. The intimal thickness was measured at 20 random points at even intervals around the circumference of each section using computerized videometric analysis (Innovision 150; American Innovision Inc., San Diego, CA); mean thickness for each graft segment was calculated from two separate sections.

In Vitro *Isometric Tension Studies*

Vein graft rings from control and captopril-treated animals were suspended from stainless steel hooks in an organ bath containing oxygenated Krebs solution of the following composition: 122 mmol/L NaCl, 4.7 mmol/L KCl, 1.2 mmol/L $MgCl_2$, 2.5 mmol/L $CaCl_2$, 15.4 mmol/L $NaHCO_3$, 1.2 mmol/L KH_2PO_4, and 5.5 mmol/L glucose. The solution was maintained at 37 C and bubbled with a mixture of 95% O_2 and 5% CO_2. One hook was fixed to the bottom of the bath and the other connected to a force transducer (Myograph F-60; Narco Bio-Systems, Houston, TX). Responses were recorded on a multi-

channel polygraph (Physiograph MK-111-S; Narco Bio-Systems). The optimal resting tension for each ring was determined by its maximal response to a modified oxygenated Krebs solution containing 60 mmol/L KCl, 66.7 mmol/L NaCl, 1.2 mmol/L $MgCl_2$, 2.5 mmol/L $CaCl_2$, 15.4 mmol/L $NaHCO_3$, 1.2 mmol/L KH_2PO_4, and 5.5 mmol/L glucose at resting tensions ranging from 0.4 to 2.5 g. The optimal resting isometric tension was applied and the tissue allowed to equilibrate in physiologic Krebs solution for 1 hour. The remainder of the experiments were performed at each ring's specific optimal resting tension.

Norepinephrine (NE; Sigma Chemical Co., St. Louis, MO), dissolved in 10^{-3} mol/L HCl, was added in a cumulative manner to each organ bath chamber and the responses were recorded. After washout and re-equilibration for 45 minutes, dose–response curves were similarly obtained in response to histamine (HIST), angiotensin I (AI), angiotensin II (AII), and serotonin (5-HT; all from Sigma; all dissolved in distilled H_2O). To avoid tachyphylaxis to either AI or AII, half the segments in each group were tested with only one of these agonists.

Statistics

The isometric responses of the rings were subsequently converted to percent maximal response to yield standard dose–response curves. The dose–response relationship was analyzed using logistic analysis to facilitate median effective dose (ED_{50}) calculation.[18] The maximal response of each ring was expressed as grams of isometric tension developed.

All data are expressed as the mean ± standard error of the mean. Differences in means were tested for significance using two-tailed Student's t test for unpaired data with p values < 0.05 regarded as significant.

Results

All animals survived the procedure and all grafts were patent at the time of harvesting. There was no significant difference in mean arterial pressure between the control and captopril-treated animals. The optimal resting tension for the control grafts (0.99 ± 0.06 g) was significantly greater than the optimal resting tension for the captopril-treated grafts (0.75 ± 0.01 g; $p < 0.001$).

Intimal Thickness

All grafts in both groups exhibited some degree of intimal hyperplasia consisting of smooth muscle proliferation, the formation of a neo-intima, and the deposition of collagen and elastin in both the intima and media (Fig. 1). Morphometrically determined intimal thickness of the

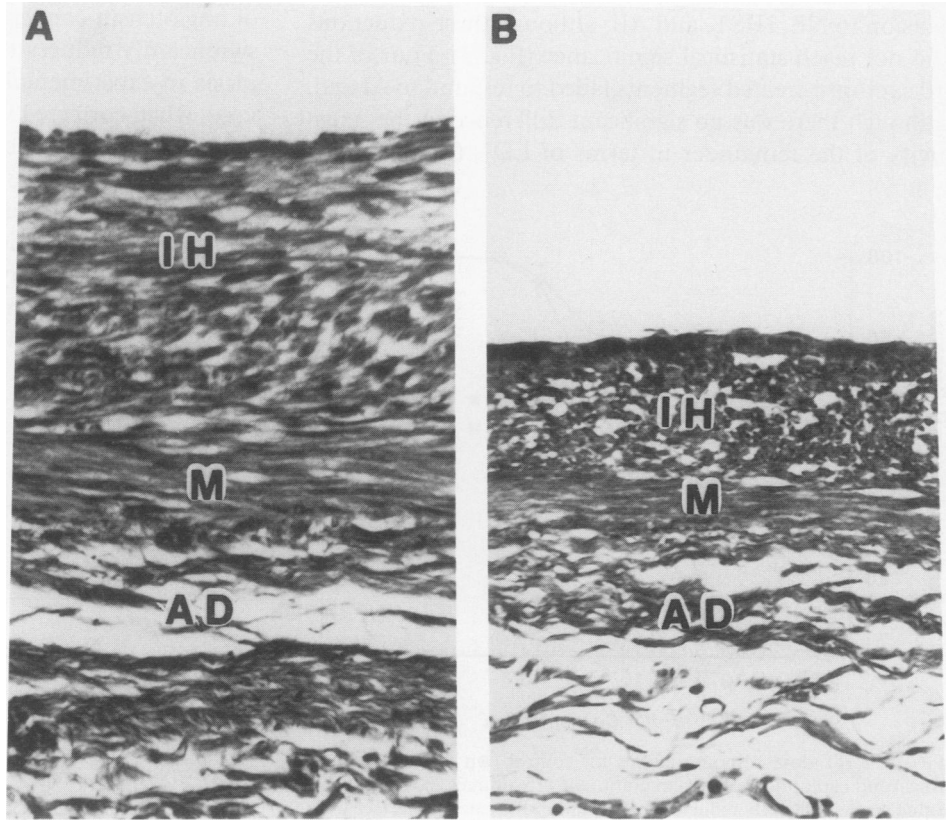

FIG. 1. A, Control vein graft showing the degree of intimal hyperplasia after 4 weeks. B, captopril-treated vein graft, with approximately 40% reduction in intimal thickness. Modified Masson's trichrome and Verhoeff's elastic tissue stains (IH, intimal hyperplasia; M, media; AD, adventitia). Original magnification ×200.

TABLE 1. *Effect of Captopril on Vein Graft Intimal Thickness*

Segment	Control Group (μm)	Captopril-treated Group (μm)	p
Proximal	156 ± 5	90 ± 4	<0.0001
Middle	150 ± 8	95 ± 5	<0.0001
Distal	151 ± 7	88 ± 3	<0.0001

grafts in the captopril-treated group was significantly less than controls in each of the proximal, middle, and distal segments (Table 1). Overall intimal thickness of the captopril-treated grafts was reduced by 40.3% as compared with controls.

In Vitro *Isometric Tension Studies*

With regard to vasomotor function, all grafts responded in classic "sigmoid" fashion to all agonists. The grafts from the captopril-treated animals were hypersensitive to *5-HT* (control ED_{50} $1.1 \pm 0.2 \times 10^{-6}$ mol/L *vs.* captopril-treated $5.5 \pm 0.5 \times 10^{-7}$ mol/L; $p < 0.005$, Fig. 2). The maximal response to *5-HT* in captopril-treated grafts, however, was significantly less than controls (control 1.6 ± 0.3 g *vs.* captopril-treated 0.8 ± 0.1 g; $p < 0.05$, Fig. 3).

Vein graft sensitivities to the other agonists are shown in Table 2. There were no significant differences in sensitivities in response to NE, HIST, AI, or AII. The captopril-treated group exhibited mild reductions in maximal tension to NE, HIST, and AII, although these reductions did not reach statistical significance (Fig. 3). Four of the 10 captopril-treated segments failed to respond to AI and, although there was no significant difference in the sensitivity of the remainder in terms of ED_{50} (Table 2), the maximal response was significantly reduced from 0.47 ± 0.06 g in the control group to 0.20 ± 0.05 g in the captopril-treated group ($p < 0.02$, Fig. 3).

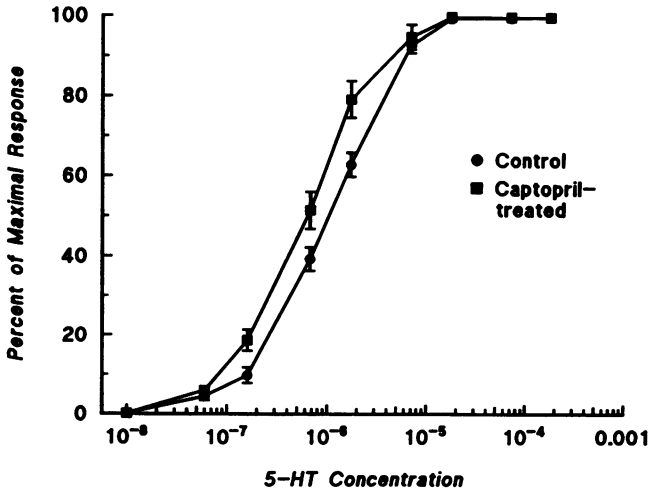

FIG. 2. 5-HT dose-response curves for control (●n = 5 animals, 20 rings) and captopril-treated vein grafts (■n = 5 animals, 20 rings). ED_{50} value was significantly reduced for the captopril-treated grafts (see text).

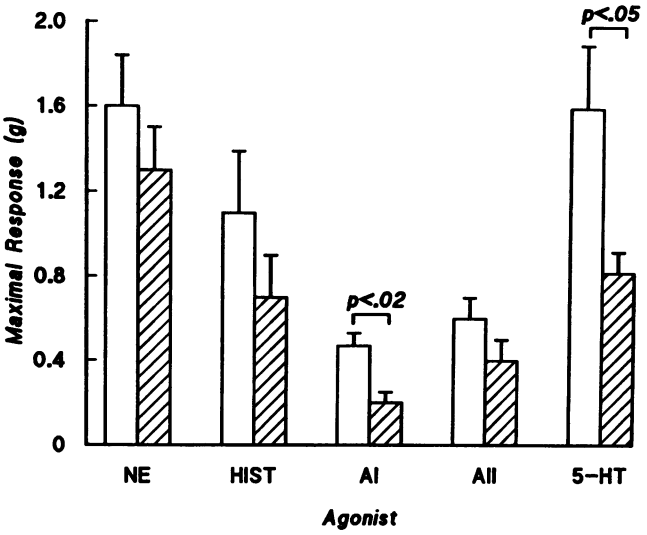

FIG. 3. Maximal response of control (open bars) and captopril-treated (hatched bars) vein grafts to norepinephrine (NE), histamine (HIST), angiotensin I (AI), angiotensin II (AII), and serotonin (5-HT). Significant reductions in maximal tension were noted with respect to AI ($p < 0.02$) and 5-HT ($p < 0.05$).

Discussion

The results of this study show that chronic inhibition of angiotensin-converting enzyme (ACE) with captopril significantly reduces the development of intimal hyperplasia in experimental vein grafts. The dose of captopril used, when corrected for body weight, was approximately twice that typically used in humans. It has been shown, however, that rabbits require up to 10 times the dose of captopril to achieve an equivalent degree of ACE inhibition generally attained in humans.[19] Thus the observed reduction in intimal hyperplasia was achieved with a dose of captopril equivalent to about 20% that typically used in patients. The relatively low dose of captopril employed herein is further illustrated by the fact that the mean arterial pressures of the control and captopril-treated groups were not statistically different.

The reduction in intimal hyperplasia was approximately 40% in all vein graft segments. This is, to our knowledge,

TABLE 2. *Vein Graft Sensitivity*

Agonist	Control Group (M)	Captopril-treated Group (M)	p
Norepinephrine	$7.8 \pm 2.5 \times 10^{-6}$	$7.9 \pm 2.8 \times 10^{-6}$	NS
Histamine	$4.0 \pm 1.0 \times 10^{-5}$	$3.4 \pm 1.2 \times 10^{-5}$	NS
Angiotensin I	$1.6 \pm 0.3 \times 10^{-7}$	$2.0 \pm 1.1 \times 10^{-7}$	NS
Angiotensin II	$3.1 \pm 0.7 \times 10^{-8}$	$2.6 \pm 0.7 \times 10^{-8}$	NS

the first demonstration of the ability of a systemically administered ACE inhibitor to attenuate intimal hyperplasia in vein grafts. A reduction in intimal hyperplasia has, however, been observed in other models. Neo-intima formation has been shown to be reduced up to 80% in intimally injured rat carotid arteries by administration of angiotensin-converting enzyme inhibitors.[13] The medial hyperplasia that has been observed in the vessels of spontaneously hypertensive rats also can be significantly reduced by ACE inhibition, whereas other anti-hypertensive agents are ineffective.[20] Lastly captopril has also been shown to have anti-atherogenic effects in heritable hyperlipidemic rabbits and cholesterol-fed monkeys.[14,15]

The mechanisms responsible for the reduction in intimal hyperplasia in this study are speculative. Captopril has a wide range of pharmacologic effects, including (1) ACE inhibition reducing local and systemic levels of angiotensin II, with consequent hypotension,[21] (2) free radical scavenging activity,[22] and (3) reduction of sympathetic nervous system activity,[21] and (4) anti-platelet activity.[23]

Angiotensin II has been shown to induce hypertrophy in cultured aortic smooth muscle cells,[10–12] and to augment proliferation of NIH 3T3 cells stimulated by epidermal growth factor.[24] The effect appears to be associated with increased expression of the proto-oncogenes c-*fos* and c-*myc* as well as the production of the A chain of PDGF. In addition the *mas* oncogene has been shown to encode a functional angiotensin II receptor.[25] Angiotensin II significantly increases DNA synthesis in cells transfected with this gene. Because experimental vein grafts have been shown to exhibit increased local ACE activity,[26] it is possible that smooth muscle cell proliferation could be locally mediated by angiotensin II and consequently reduced by ACE inhibition.

Captopril, unlike other ACE inhibitors, contains a sulfhydryl (SH) group and can act as a free radical scavenger.[22] Sulfhydryl-containing ACE inhibitors have been shown to protect cultured endothelial cells from free radical injury.[27] In addition the superoxide dismutase mimic, desferrioximine Mn^{3+}, has been shown to reduce intimal hyperplasia in the same experimental vein graft model used in this study.[28] Further studies employing non–sulfhydryl-containing ACE inhibitors may show if this mechanism is important in modulating intimal hyperplasia.

Captopril is a potent antihypertensive agent.[21] Many antihypertensive drugs have been shown to inhibit intimal hyperplasia or atherogenesis, including calcium antagonists, prazosin, and β-blockers.[29–31] The captopril dose used in this study did not significantly reduce blood pressure, however, so this mechanism is unlikely to be responsible for the observed effect. Captopril also has been shown to reduce sympathetic nervous system activity.[21] This effect could reduce effect the development of intimal hyperplasia because α-adrenoreceptor antagonism has been shown to reduce intimal hyperplasia in balloon-injured aorta.[30] Because there was no difference between control and experimental grafts' response to norepinephrine, however, and because these vessels are denervated in the process of grafting, it is unlikely that captopril's sympatholytic properties were involved.

Chronic ACE inhibition had several effects on the vasomotor function of vein grafts in this study. Vein grafts from captopril-treated animals exhibited decreased optimal resting tension as well as attenuated maximal active tension in response to AI and 5-HT. In addition the maximal contraction in response to all tested agonists (NE, HIST, AI, AII, and 5-HT) tended to be reduced (Fig. 3). The reduced optimal resting tension and maximal active tension probably reflect the reduction of smooth muscle cells in captopril-treated grafts.

The increased sensitivity to 5-HT in the experimental group was an unexpected finding. The importance of the interaction between 5-HT and the vascular system has only recently been recognized. Rabbit jugular vein does not constrict in response to 5-HT but, after grafting into the arterial circulation, develops 5-HT_2 receptor-mediated contraction.[32–34] The sensitivity of vein grafts to 5-HT does not change once developed despite significant increases in the degree of intimal hyperplasia.[33] There is no apparent explanation for the observed increase in vein graft 5-HT sensitivity after captopril treatment, although it is tempting to postulate that modulation of platelet function by captopril[23] could deprive the developing cells of a source of 5-HT, thereby inducing supersensitivity.

In summary the results of this study indicate that captopril can significantly reduce intimal hyperplasia and alter vasoreactivity in experimental vein grafts. This may be due to inhibition of smooth muscle proliferation by local renin-angiotensin systems or to free radical scavenging effects. The dose used was equivalent to 20% that typically prescribed for humans and did not significantly affect systemic blood pressure. It is concluded that ACE inhibitors may have therapeutic applications in patients undergoing vein bypass graft procedures.

Acknowledgments

The authors wish to acknowledge the excellent technical assistance of Liz Barber and Patsy Tidwell. In addition, they thank E. R. Squibb and Son for providing captopril, and Ethicon, Inc. for providing microvascular suture.

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