JACC Vol. 25, No. 5
April 1995:1089–96

Combined Captopril and Isosorbide Dinitrate During Healing After Myocardial Infarction

Effect on Ventricular Remodeling, Function, Mass and Collagen

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Objectives. **We sought to compare the effects of captopril plus isosorbide dinitrate versus monotherapy on infarct collagen content and left ventricular remodeling and function during healing after myocardial infarction.**

Background. **Captopril or isosorbide dinitrate monotherapy can limit postinfarction dilation. Whether captopril inhibits infarct collagen content, or whether captopril plus isosorbide dinitrate might be more beneficial, is not known.**

Methods. **In vivo remodeling variables and function (echocardiography), hemodynamic variables, postmortem topography (planimetry) and collagen content (hydroxyproline) were measured in 48 chronically instrumented dogs that were randomized 2 days after left anterior descending coronary artery ligation to 6 weeks of therapy with captopril, isosorbide dinitrate, captopril plus isosorbide dinitrate or placebo.**

Results. **Compared with placebo, the three active therapies decreased blood pressure and left atrial pressure; limited infarct expansion, infarct thinning, noninfarct wall stretching and thickening; limited left ventricular dilation and increase in left ventricular mass; and decreased regional bulging, aneurysm frequency and left ventricular dysfunction. However, the decrease in asynergy and increase in volume ejection fraction were less with captopril or captopril plus isosorbide dinitrate than with isosorbide dinitrate. Infarct thinning and bulging at 6 weeks was also less with isosorbide dinitrate than with captopril. Although initial left ventricular asynergy, final scar sizes and noninfarct collagen content at 6 weeks were similar among the groups, collagen in the center of the infarct scar was less with captopril or captopril plus isosorbide dinitrate than with placebo or isosorbide dinitrate.**

Conclusions. **Monotherapy with captopril or isosorbide dinitrate, or their combination, improved all remodeling variables, but isosorbide dinitrate improved function more than captopril or captopril plus isosorbide dinitrate. Inhibition of infarct collagen content by captopril suggests that benefits with captopril represent a balance between positive and negative effects, and its combination with isosorbide dinitrate might be advantageous.**

(J Am Coll Cardiol 1995;25:1089–96)

Structural remodeling of infarct and noninfarct regions during healing after myocardial infarction (1) contributes to left ventricular dilation and dysfunction and decreased survival (2,3). Prolonged left ventricular unloading after infarction, by reducing wall stress, can limit remodeling, prevent chamber dilation and preserve function (4,5). These results were achieved with the angiotensin-converting enzyme inhibitor captopril in rats (6), dogs (7,8) and humans (9) and translated into survival benefit in rats (10) and humans (11). However, recent reports indicate that captopril (12), other angiotensin-converting enzyme inhibitors (13) and angiotensin II receptor blockade (14) decrease noninfarct collagen content. Long-term unloading with nitrate therapy, in dose regimens to minimize tolerance, also limits remodeling and improves function (5) and decreases ventricular distensibility and rupture threshold (15) in dogs. However, nitrate therapy does not decrease infarct or noninfarct collagen content at 1 or 6 weeks (5,15); rather, it increases infarct collagen at 1 week (16). Because captopril can potentially decrease infarct collagen content (12,17,18) and donate sulfhydryl radicals (19) that are depleted during long-term nitrate therapy (20), and both nitrates (21,22) and angiotensin-converting enzyme inhibitors (23,24) exert local vascular and tissue effects that might show synergism, the combination of captopril and nitrate might prove more beneficial than monotherapy.

The present study therefore compared the effects of combined therapy with captopril and isosorbide dinitrate versus monotherapy on remodeling and function as well as infarct and noninfarct collagen content during postinfarct healing in a well defined dog model (5,7).

From the Cardiology Division, Department of Medicine, University of Alberta and University of Alberta Hospital, Edmonton, Alberta, Canada. This study was supported in part by grants from the Medical Research Council of Canada and the Canadian Heart and Stroke Foundation, Ottawa, Ontario. It was performed during the tenure of Dr. Jugdutt as a Scientist of the Alberta Heritage Foundation for Medical Research, Edmonton, Alberta, Canada. It was presented in part at the 66th Annual Scientific Sessions of the American Heart Association, Atlanta, Georgia, November 1993.

Manuscript received September 7, 1994; revised manuscript received November 15, 1994, accepted November 29, 1994.

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0735-1097/95/$9.50
0735-1097(94)00531-T

JACC Vol. 25, No. 5
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Methods

Experimental preparation. The experiments were approved by the institutional animal welfare committee and conformed to the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 1984. Sixty healthy mongrel dogs (16 to 29 kg) of either gender were chronically instrumented through a left lateral thoracotomy under general anesthesia (sodium pentobarbital, 30 mg/kg body weight intravenously), as previously described (5,7). Polyethylene catheters were inserted in the external jugular vein, internal carotid artery and left atrium, filled with heparinized saline solution, and their ends exteriorized behind the neck. The mid-left anterior descending coronary artery was ligated with silk. Pairs of metal beads were sutured on anterior, lateral and posterior surfaces of the left ventricular epicardium in the short-axis plane at the mid-occluded bed for consistent echocardiographic imaging. After closure of the pericardium and chest, penicillin (1 million U) and streptomycin (1 g) were given intramuscularly.

Protocol. Two days after ligation, 52 healthy survivors were randomized to four treatment groups (13 each) using a factorial design: placebo twice a day; captopril 50 mg twice a day; isosorbide dinitrate 30 mg twice a day on an eccentric 8 AM, 4 PM schedule to allow a washout phase; and captopril twice a day plus isosorbide dinitrate twice a day. The dogs were given free access to fluids, and no attempt was made to treat heart failure. At 6 weeks, the 48 surviving dogs were anesthetized, and the hearts were arrested in diastole with an overdose of intravenous potassium chloride and excised, washed in normal saline solution and weighed.

In vivo measurements during healing. As described previously (5,7), two-dimensional echocardiograms (Toshiba SSH-65A; 3.5-MHz transducer), electrocardiograms (Gould recorder) and hemodynamic variables (Statham P23Db for left atrial and arterial pressures) were recorded at eight intervals in conscious dogs standing in a sling for support as follows: before therapy at 2 days, weekly during therapy and again after therapy and before they were killed. Recordings were made 3 to 4 h after the first daily doses. Echocardiograms were also obtained before and after surgery. Standard parasternal long- and short-axis views of the mitral, chordal, low and mid-papillary and apical levels and apical four- and two-chamber views were used.

Analysis of echocardiograms. As described previously (5,7), coded echocardiograms were analyzed in double-blind manner on video playback (0.5-in. tapes) by two independent observers, and differences were resolved by consensus. Briefly, endocardial and epicardial outlines of left ventricular images at end-diastole and end-systole were traced with a light pen (Diasonics CardioRevue Center) and copied on plastic overlays. Anatomic landmarks such as papillary muscles were indicated on the tracings. Asynergy, defined as akinesia (no systolic inward motion and thickening) or dyskinesia (systolic outward motion and thinning), or both, was marked on each endocardial diastolic outline. The circumferential extent of asynergy on each short-axis outline was then digitized (Hewlett-Packard models 9878A and 9835A) and used to compute total endocardial surface area asynergy by a three-dimensional reconstruction algorithm. Outlines from five short-axis and two long-axis views were used to compute volumes by means of a modified Simpson rule algorithm. Global ejection fraction was calculated as end-diastolic volume minus end-systolic volume divided by end-diastolic volume. Interobserver error was $<5\%$ in marking asynergy, segment length, wall thickness and areas of outlines, in agreement with previous studies (5,7). Topographic measurements were made on end-diastolic outlines of papillary short-axis images, and expansion index (ratio of the lengths of asynergy-containing and nonasynergy-containing segments), thinning ratio (ratio of average thicknesses of asynergic and nonasynergic zones) and regional area ejection fraction (end-diastolic area minus end-systolic area divided by end-diastolic area) were computed. Regional bulging of the asynergic zone was characterized by its area and depth, as described previously (5,7,8). Left ventricular aneurysm was defined as a bulging in diastole and further bulging in systole. Left ventricular mass was calculated from the volume of myocardium (difference in volumes of epicardial and endocardial shells at end-diastole) multiplied by an assumed specific gravity of 1.05 g/ml.

Postmortem measurement of scar size, geometry and collagen content. As described previously (5,7), the risk region was measured on postmortem coronary arteriograms recorded on whole-heart and transverse section (1 to 1.5 cm thick) radiographs. Outlines of weighed left ventricular rings, risk regions and infarct scars were made on plastic overlays and subjected to computerized planimetry (Hewlett-Packard 9835A computer and 9874A digitizer interfaced with a VAX 750 computer) for infarct size and topography, including "thinning" ratio (ratio of average thickness of infarcted wall to average thickness of the normal wall) and "expansion" index (ratio of endocardial lengths of infarct-containing to noninfarct-containing segments demarcated by papillary muscles), and short-axis topographic maps were made for each group (5,7). Contours of the left ventricular epicardium and endocardium from whole-heart radiographs were digitized to measure the area and depth of the apical bulge and construct topographic long-axis maps for each group (5,7). Histopathologic studies for extent of infarction and collagen content (1) were performed using a 5-mm slice from the middle of the infarct zone and triplicate 5-μm thick sections that were stained with hematoxylin-eosin, Mallory's stain or Masson's trichrome, respectively. Myocardial hydroxyproline (mg/g dry tissue weight), a marker for collagen, was measured in 100 to 200 mg samples from center and border regions of the infarct scar, after excising visually normal tissue on gross examination, and the noninfarct center (1,16).

Statistics. Data were analyzed in blinded manner. The statistical tests used were 1) analysis of variance (univariate) for differences within and between separate or combined groups; 2) repeated measures analysis of variance with orthogonal contrast for comparing serial data within groups and a

multigroup repeated measures design for overall differences between groups; 3) multiple comparisons analysis of variance and the Student Newman-Keuls test for the significance between placebo and separate or combined therapy groups; and 4) chi-square and Fisher exact tests for the significance of difference in event frequency among groups. The main predefined comparisons were captopril versus placebo, isosorbide dinitrate versus placebo and captopril plus isosorbide dinitrate versus placebo. Results are presented as mean value ± SD unless otherwise stated. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Study groups. Of the 52 dogs that were randomized, one from each group died. Data from the 48 survivors that were killed at 6 weeks (12 in each group) form the basis of this report.

Hemodynamic changes. The 2-day pretreatment values were similar among the groups, with average values for all 48 dogs as follows: heart rate 138 ± 26 beats/min, mean arterial pressure 112 ± 15 mm Hg and left atrial pressure 15 ± 4 mm Hg. Baseline variables measured 3 to 4 h after treatment showed no change with placebo but significant decreases ($p < 0.005$) in atrial (11%) and arterial (9%) pressure with the active drugs. In Figure 1 (points in Fig. 1 to 6 are offset around time lines for clarity), most atrial and arterial pressures decreased further over the 6 weeks. Compared with placebo at 6 weeks, the combined active therapy groups showed a greater decrease in atrial pressure (−33% vs. −15%, $p < 0.05$) and arterial pressure (−11% vs. +3%, $p < 0.025$) but no significant decrease in heart rate (−28% vs. −41%, $p < 0.2$). The decrease in atrial pressure over the 6 weeks was more pronounced with isosorbide dinitrate (Fig. 1). Mild increases ($p \leq 0.05$) in atrial and arterial pressures were seen after drug withdrawal at 6 weeks (Fig. 1).

Changes in infarct and noninfarct wall stretch. For all 48 dogs, mean anterior and posterior segment lengths were 8.7 ± 1.4 and 4.2 ± 0.2 cm, respectively, preocclusion and 11.2 ± 1.5 and 4.6 ± 0.8 cm, respectively, at the 2-day baseline, indicating predominant elongation of the infarct segment by day 2. There was no difference in these baseline variables among groups. However, all active therapies prevented elongation of infarct- and noninfarct-containing segments and decreased the expansion index over the 6 weeks compared with placebo (Fig. 2).

Changes in infarct and noninfarct wall thickness. For all 48 dogs, the mean anterior and posterior wall thicknesses were 0.95 versus 0.95 cm preocclusion and 0.65 ± 0.11 versus 0.97 ± 0.11 cm ($p < 0.001$) at the 2-day baseline, indicating infarct wall thinning by day 2. These baseline thicknesses did not differ among the groups. However, all active therapies attenuated the infarct wall thinning and noninfarct wall thickening seen over the 6 weeks with placebo (Fig. 3). In addition, the change in infarct wall thickness at 6 weeks was slightly higher for isosorbide dinitrate than captopril (+12% vs. +4%, $p < 0.05$) or for captopril plus isosorbide dinitrate than captopril (+12% vs. +4%, $p < 0.05$), indicating less thinning with isosorbide dinitrate or captopril plus isosorbide dinitrate than with captopril.

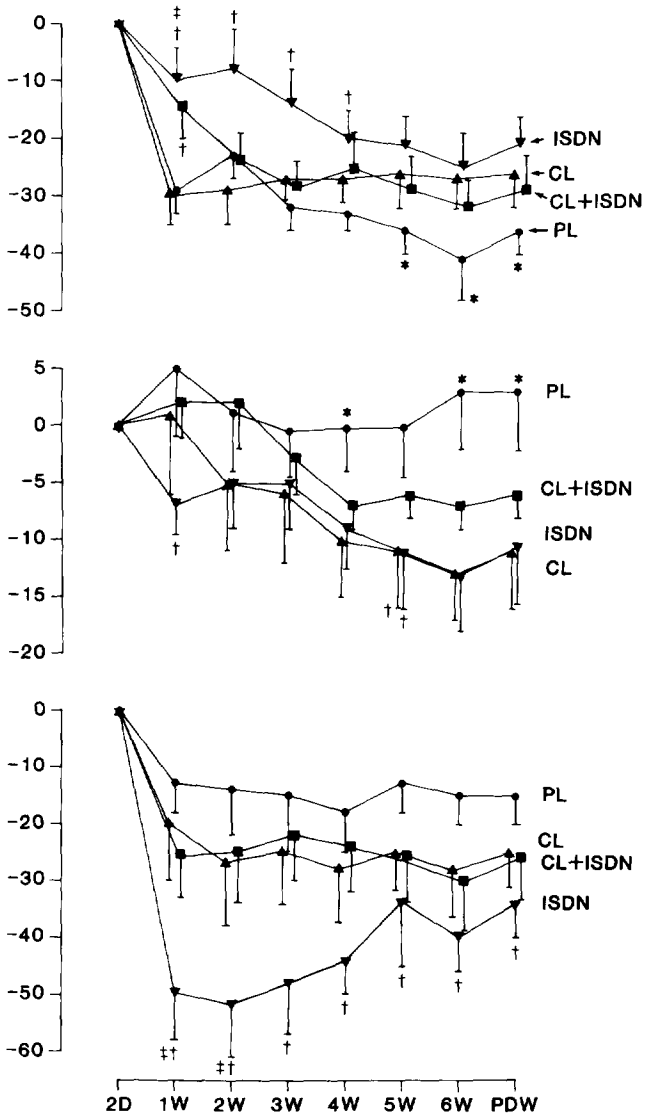


Figure 1. Percent changes in heart rate (**top**), arterial pressure (**middle**) and left atrial pressure (**bottom**). CL = captopril; D = day; ISDN = isosorbide dinitrate; PDW = after drug withdrawal; PL = placebo; W = week. *$p \leq 0.05$, placebo versus active therapy. †$p \leq 0.05$, least significant difference, isosorbide dinitrate or captopril plus isosorbide dinitrate versus placebo. ‡$p < 0.05$, isosorbide dinitrate versus captopril. Data shown are mean value ± SEM.

Changes in regional bulging and aneurysm frequency. All active therapies decreased diastolic bulging of asynergic zones compared with placebo. Thus, the decrease in area of the bulge was greater with active therapies than placebo (−82% vs. −5%, $p < 0.001$). The frequency of ventricular aneurysm was lower with captopril (3 of 12 vs. 12 of 12, chi-square 11.38, $p < 0.001$), isosorbide dinitrate (0 of 12 vs. 12 of 12, chi-square 20.17, $p < 0.001$) and captopril plus isosorbide dinitrate (0 of 12 vs. 12 of 12, chi-square 20.17, $p < 0.001$) than placebo but

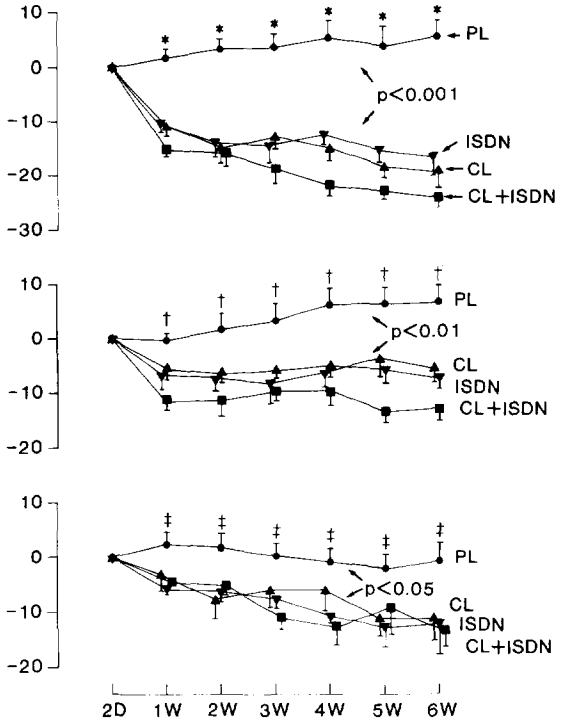


Figure 2. In vivo percent changes in anterior **(top)** and posterior **(middle)** segment lengths and infarct expansion **(bottom)**. *p < 0.001, †p < 0.01, ‡p < 0.05, placebo versus active therapy; **p values between plots** = placebo versus active therapy groups combined. Abbreviations as in Figure 1. Data shown are mean value ± SEM.

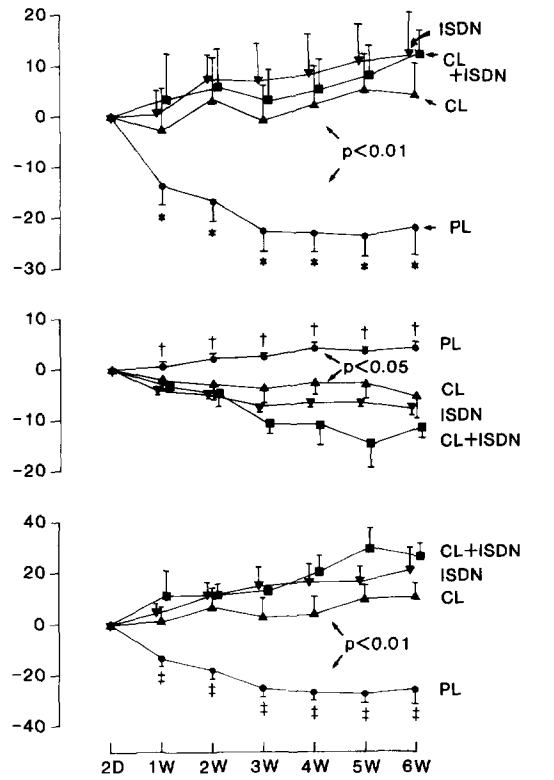


Figure 3. In vivo percent changes in anterior **(top)** and posterior **(middle)** wall thicknesses and infarct thinning **(bottom)**. *p < 0.01, †p < 0.05, ‡p < 0.01, placebo versus active therapy groups; **p values between plots** = placebo versus active therapy groups combined. Abbreviations as in Figure 1. Data shown are mean value ± SEM.

was not different between captopril and isosorbide dinitrate groups (3 of 12 vs. 0 of 12, p > 0.15).

Changes in ventricular dilation. There was no difference in baseline diastolic and systolic volumes or diastolic endocardial surface area among the groups at 2 days; mean values for the 48 dogs were 80 ± 23 and 45 ± 17 ml and 85 ± 18 cm^2, respectively. However, all active therapies limited the progressive increase in diastolic and systolic volumes and diastolic surface area found with placebo between 2 days and 6 weeks (Fig. 4). Changes in diastolic and systolic areas (papillary level) were similar to changes in volumes.

Changes in left ventricular mass. Baseline mass at 2 days was similar among the groups and averaged 90 ± 10 g for all 48 dogs. However, all active therapies limited the increase in mass found with placebo between 2 days and 6 weeks, and the magnitude of the effect was similar among therapy groups (Fig. 5).

Changes in regional and global left ventricular function. There was no difference in baseline circumferential asynergy, endocardial surface area of asynergy, area ejection fraction or volume ejection fraction among the groups at 2 days, and the values for all 48 dogs were 29 ± 8%, 22 ± 10%, 31 ± 8% and 45 ± 7%, respectively. However, all active therapies decreased regional dysfunction and improved global systolic function between 2 days and 6 weeks compared with placebo (Fig. 6). There was greater improvement (p < 0.05) in both regional and global systolic function with isosorbide dinitrate than captopril or their combination (Fig. 6).

Postmortem scar size. There were no statistically significant differences in the mass of the scar, left ventricle or risk region in the groups at 6 weeks (Table 1). No differences in standard histologic studies of scar tissue were detected among the groups.

Postmortem topography. Average short-axis maps at the low papillary level showed less cavity area, infarct wall thinning and noninfarct wall thickness with active therapies than placebo (Table 2). However, the infarct scar wall was slightly thicker with isosorbide dinitrate than captopril and captopril plus isosorbide dinitrate. Despite equal infarct scar areas among therapy groups, the transmural extent was less with captopril, suggesting a flattening of the scar. Average long-axis maps showed less apical bulging, smaller cavity areas and less apical scar thinning with active therapies than placebo (Table 2). The bulge and scar thinning were slightly less with isosorbide dinitrate than captopril and captopril plus ISDN.

Effect on regional collagen. Noninfarct collagen content was similar among the groups, but infarct collagen content differed considerably (Fig. 7). As noted previously (5,7,8), collagen content was greater in the center (p < 0.001) and border (p < 0.05) of the infarct than in the noninfarct region for each group. However, collagen content in the infarct center

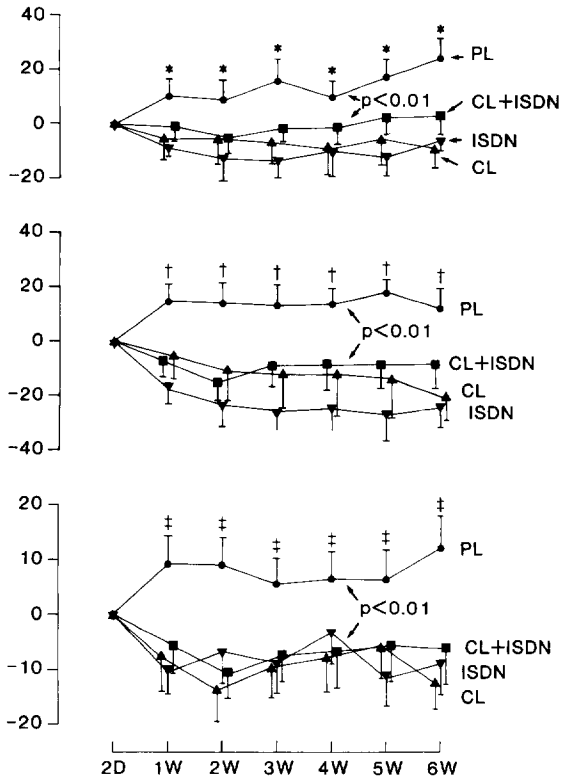
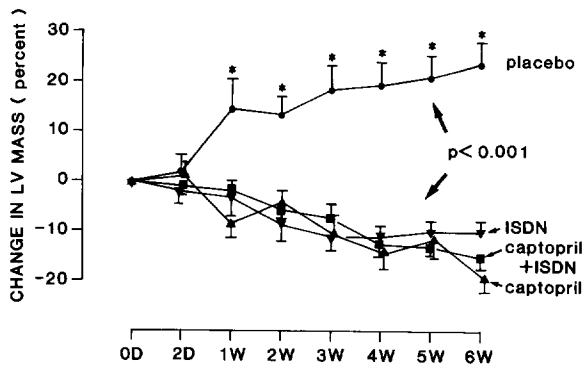


Figure 4. In vivo percent changes in end-diastolic (**top**) and end-systolic (**middle**) volumes and surface area (**bottom**). *†‡p < 0.01, placebo versus active therapy; **p values between plots** = placebo versus active therapy groups combined. Abbreviations as in Figure 1. Data shown are mean value ± SEM.

and border regions for isosorbide dinitrate did not differ from that for placebo but were significantly less for captopril and captopril plus isosorbide dinitrate (Fig. 7). The increase in collagen in the infarct center with placebo was similar to that with isosorbide dinitrate (994% vs. 1,056%, p > 0.51) but significantly greater than that with captopril (994 ± 504% vs. 507 ± 282%, p < 0.01) or captopril plus isosorbide dinitrate (994 ± 504% vs. 388 ± 289%, p < 0.005). The increase in

Figure 5. In vivo percent changes in left ventricular (LV) mass. *p < 0.001, placebo versus active therapy; **p value between plots** = placebo versus active therapy groups combined. Abbreviations as in Figure 1. Data shown are mean value ± SEM.



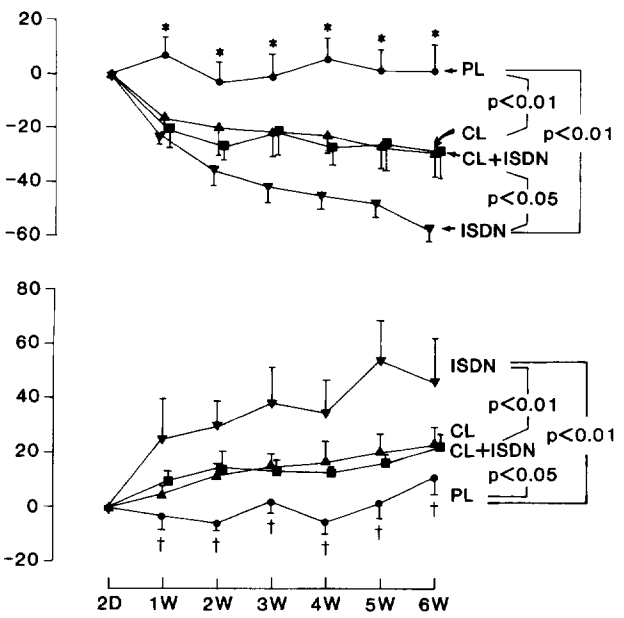


Figure 6. In vivo percent changes in regional ventricular dysfunction (**top**) and volume ejection fraction (**bottom**). *†p < 0.01, placebo versus active therapy groups; **p values at right** = placebo versus isosorbide dinitrate, and placebo or isosorbide dinitrate versus captopril and captopril plus isosorbide dinitrate. Abbreviations as in Figure 1. Data shown are mean value ± SEM.

collagen in the infarct center was also greater with isosorbide dinitrate than captopril (1056 ± 600% vs. 507 ± 282%, p < 0.025) or captopril plus isosorbide dinitrate (1056 ± 600% vs. 388 ± 289%, p < 0.005). The trend was similar for the scar border region.

Discussion

There are three new findings in this study: 1) Combination therapy with captopril plus isosorbide dinitrate and monotherapy with captopril or isosorbide dinitrate had a similar beneficial effect on several in vivo variables of remodeling between 2 days and 6 weeks after canine anterior myocardial infarction. Thus, compared with placebo, all active therapies limited infarct segment stretching, infarct wall thinning, enlargement of left ventricular diastolic and systolic volumes, increase in noninfarct segment length and wall thickness, increase in end-diastolic endocardial surface area, increase in left ventricular mass, bulging of the infarct zone and aneurysm formation.

2) The active therapies improved regional and global systolic function compared with placebo, but the decrease in asynergy and improvement in ejection fraction were greater with isosorbide dinitrate than with captopril or captopril plus isosorbide dinitrate.

3) Collagen content in the center of the infarct scar at 6 weeks was lower with captopril or captopril plus isosorbide dinitrate compared with isosorbide dinitrate or placebo. This effect was associated with slightly greater preservation of

Table 1. Infarct Scar Size (mean ± SD) in the Four Study Groups

	Placebo (n = 12)	Captopril (n = 12)	ISDN (n = 12)	Captopril + ISDN (n = 12)	p Value
Infarct scar mass (g)	6.0 ± 2.1	4.0 ± 3.6	5.9 ± 4.5	4.8 ± 2.0	0.76
Risk region mass (g)	13.3 ± 4.1	14.8 ± 5.6	15.8 ± 8.2	11.4 ± 4.2	0.56
LV mass (g)	76.2 ± 16.1	80.8 ± 8.5	79.3 ± 14.6	80.8 ± 14.0	1.64
Infarct scar/risk (%)	46.4 ± 13.9	28.7 ± 22.9	35.3 ± 19.6	45.1 ± 18.8	0.17
Risk/LV mass (%)	17.7 ± 5.3	18.6 ± 7.8	20.0 ± 11.1	14.4 ± 5.2	0.69
Infarct/LV mass (%)	7.8 ± 1.9	5.1 ± 4.8	7.4 ± 5.8	6.1 ± 2.5	0.71

ISDN = isosorbide dinitrate; LV = left ventricular.

infarct wall thickness and less bulging at 6 weeks with isosorbide dinitrate or captopril plus isosorbide dinitrate than with captopril.

Mechanisms. Several factors might have contributed to the therapeutic benefit: 1) Vasodilation, left ventricular unloading and reduced diastolic stress probably played a major role because arterial and especially left atrial pressures measured 3 to 4 h after drug therapy were mostly lower, left ventricular chamber size was smaller, and regional bulging was less with active therapy than placebo. Current evidence suggests that isosorbide dinitrate produces vasodilation by donating nitric oxide (25), stimulating guanylate cyclase and increasing cyclic guanosine monophosphate, whereas angiotensin-converting enzyme inhibitors such as captopril mediate vasodilation by decreasing bradykinin breakdown and increasing bradykinin, which releases nitric oxide (25) and prostacyclin (26). Increased nutrient flow, through dilation of coronary arteries and collateral vessels or reduced endocardial compression from diastolic unloading (4), might have provided further benefit. Because venodilation leads to decreased chamber size and diastolic wall stress (Laplace's law), which in turn decreases wall stretch, decreases gene expression of contractile and noncontractile proteins and prevents hypertrophy (23,27), this mechanism might partly explain the decrease in left ventricular mass observed with active therapy.

2) Tissue effects may be involved. Thus, the decrease in ventricular mass with nitrates (5,28) might in part be mediated by an antimyocyte hypertrophic effect of nitric oxide, similar to its known inhibition of mitogenesis and smooth muscle proliferation (21). The antihypertrophic effect of captopril appears to be mediated by inhibition of circulating angiotensin II as well as tissue angiotensin-converting enzyme inhibitors and intramyocardial conversion of angiotensin I to angiotensin-II, decreased local angiotensin II (24), angiotensin II type I receptor blockade (14) and decreased activity of both myocyte and fibroblast growth factors (13,18,29,30).

3) Effects on the supporting matrix might have contributed in limiting remodeling and preserving function. Because increased wall stress and decreased flow damage the matrix (31,32), therapy-induced decrease in diastolic wall stress and increase in nutrient flow might preserve matrix integrity. It is also possible that mechanical coupling between collagen fibrils and live myocytes at the infarct scar borders (33) was improved by the therapies, especially isosorbide dinitrate, and contrib-

Table 2. Postmortem Measurements (mean ± SD) on Average Topographic Maps

	Placebo (n = 12)	Captopril (n = 12)	ISDN (n = 12)	Captopril + ISDN (n = 12)
Short-axis map (low papillary)				
Angular extent of infarct (θ^c)	107 ± 4	88 ± 13*†	84 ± 4*‡	121 ± 6*
Infarct wall thickness (mm)	8 ± 1	8 ± 1†	10 ± 1*‡§	9 ± 1*
Noninfarct wall thickness (mm)	15 ± 1	13 ± 1*	13 ± 1*	13 ± 1*
Area of infarct scar (cm^2)	5.0 ± 0.8	3.1 ± 0.7*†	3.4 ± 0.9*	3.7 ± 0.3*
Transmural extent of scar (%)	62 ± 7	48 ± 11*	60 ± 7‡§	64 ± 6
LV cavity area (cm^2)	4.7 ± 0.9	3.4 ± 0.9*†	2.6 ± 0.7*§	2.8 ± 0.2*
Long-axis map (radiographs)				
Area of apical bulge (cm^2)				
Endocardial	1.2 ± 1.1	0.2 ± 0.1*	0.2 ± 0.2*	0.1 ± 0.1*
Epicardial	0.8 ± 0.3	0.1 ± 0.1*	0.1 ± 0.1*	0.1 ± 0.1*
Depth of apical bulge (mm)				
Endocardial	6.6 ± 2.8	3.3 ± 1.2*	2.2 ± 1.5*§	2.8 ± 1.9*
Epicardial	3.4 ± 1.6	0.8 ± 0.8*	0.7 ± 0.6*	0.8 ± 0.9*
Area of LV cavity (cm^2)	13.7 ± 3.6	11.3 ± 2.1*†	11.8 ± 2.0*‡	9.4 ± 1.2*
Apical wall thickness (mm)	4.6 ± 1.3	6.8 ± 1.5*†	8.0 ± 2.1*§	8.0 ± 2.4*

*$p \leq 0.05$, each active therapy versus placebo. †$p \leq 0.05$, captopril versus captopril plus isosorbide dinitrate (ISDN). ‡$p \leq 0.05$, isosorbide dinitrate versus captopril plus isosorbide dinitrate. §$p \leq 0.05$, isosorbide dinitrate versus captopril. LV = left ventricular.

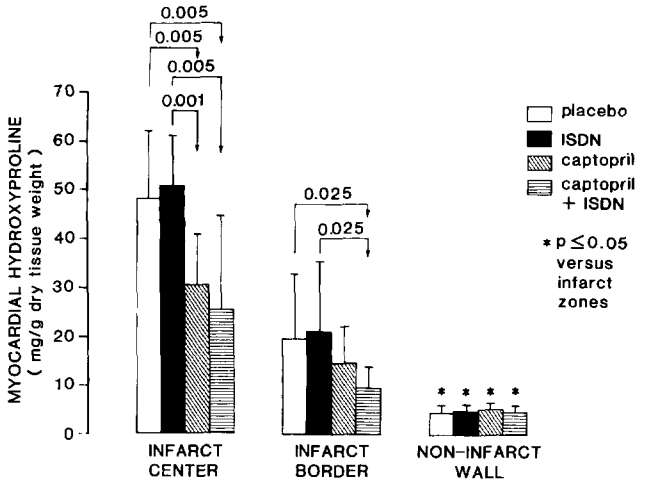


Figure 7. Bar graphs of myocardial hydroxyproline content in infarct and noninfarct regions. ISDN = isosorbide dinitrate. Data shown are mean value ± SD; **p values** indicate the difference between groups by analysis of variance.

uted to improved mechanical function. Whether the greater improvement in function with isosorbide dinitrate might have been due to the greater decrease in left atrial pressure (an index of preload), resulting in more nutrient flow and more preservation of the matrix and mechanical function, is not clear. The finding that hemodynamic effects of isosorbide dinitrate were not sustained over 24 h with the eccentric dosing suggests that intermittent unloading can influence remodeling and that other as yet poorly defined mechanisms might be operational.

Infarct collagen. To our knowledge, a decrease in infarct collagen with long-term angiotensin-converting enzyme inhibition during infarct healing, as seen with captopril in our dog infarction model, has not been previously reported. The reason why captopril decreased infarct but not noninfarct collagen content might be because angiotensin-converting enzyme inhibition is more likely to influence active collagen deposition. In the rat model, where infarctions are large, involve the entire free wall and only spare the septum, and there is marked left ventricular dilation, hypertrophy and increased collagen in the noninfarcted septum, early captopril therapy during infarct healing inhibits DNA synthesis, fibroblast proliferation and collagen deposition in noninfarct regions (12). This effect on noninfarct collagen content is also seen when the angiotensin-converting enzyme inhibitor perindopril (13) or the angiotensin II type I receptor blocking agent losartan (14) is given during and after healing but is not seen when captopril is given after healing (26). Unlike rat infarcts, the anterior infarcts in our dog model were small, mainly anteroapical and caused mild chamber dilation, and noninfarct collagen content did not increase on standard histologic or biochemical assay. However, captopril decreased collagen content in the infarct scar and altered scar topography, causing flattening, less transmural extent but similar area compared with other therapies. The decrease in collagen synthesis by captopril was probably mediated by inhibition of local effects of angiotensin II and decreased activity of fibroblast growth factor and transforming growth factor-beta$_1$, which are known to modulate extracellular matrix and stimulate collagen synthesis (34,35). Whether altered collagenase activity played a role is not known. It is possible that a decrease in infarct collagen content might allow more remodeling under the effect of mechanical forces during healing in vivo (3), especially in the setting of large transmural infarctions. Although isosorbide dinitrate did not decrease infarct collagen content, it did not prevent the decrease in infarct collagen caused by captopril. However, the preserved infarct collagen with isosorbide dinitrate might have contributed to the striking improvement in regional and global ventricular function.

Study limitations. The infarct scars in our model were small as a result of shrinkage, which decreases infarcts of ~20% of the left ventricle at day 1 to ~10% at 6 weeks (1,5). However, they were mostly subendocardial so that remodeling (36) and matrix disruption in the risk zone (37) were less severe than that seen with transmural infarctions. Because we did not measure the mechanical strength of the infarct scars (5), whether an infarct scar with less collagen might be weaker remains unanswered. Our failure to demonstrate superiority of combined therapy might in part be due to the small infarct scars and small sample sizes.

Clinical implications. The aim of therapy to limit left ventricular remodeling during infarct healing should be to decrease deformation forces and preserve shape, prevent excessive dilation, prevent excessive infarct stretching and thinning, promote healing and preserve nutrient flow, protect the supporting collagen matrix and possibly limit hypertrophy and further necrosis (3). The final outcome depends on the balance of effects. In subendocardial infarctions, an epicardial rim of normal myocardium and collagen matrix appears to act as a scaffold that resists bulging, so that decreased infarct collagen and matrix disruption might not impact as significantly on outcome as large transmural infarctions.

Conclusions. In the present study, prolonged therapy with captopril or isosorbide dinitrate, or both, during healing of relatively small anterior myocardial infarction limited remodeling and improved systolic function in vivo and improved topography at 6 weeks despite a decrease in infarct collagen content with captopril. Although captopril-induced decrease in infarct collagen might explain the lesser improvement in function compared with isosorbide dinitrate, the effect did not have a significant negative impact on in vivo remodeling variables. The overall results suggest that the benefits of angiotensin-converting enzyme inhibition represent a balance of positive and negative effects. Whether combination therapy with a nitrate might be advantageous in the setting of large anterior infarction needs further study.

We are grateful to Vijayan Menon for computing and statistics, Anil Bhambhani, Ruwan Liyanage and Michael Joljart for data processing and Catherine Graham for typing.

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