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UNIVERSITY OF ALBERTA

MODIFICATION OF POST-INFARCT REMODELING WITH THE ACE-INHIBITOR CAPTOPRIL

by

© Bogdan L. Schwarz-Michorowski, M.D.

A THESIS SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

IN

EXPERIMENTAL MEDICINE

DEPARTMENT OF MEDICINE

EDMONTON, ALBERTA

FALL, 1991

ISBN 0-315-70205-2

U N I V E R S I T Y O F A L B E R T A

RELEASE FORM

NAME OF AUTHOR: Bogdan L. Schwarz-Michorowski

TITLE OF THESIS: MODIFICATION OF POST-INFARCT REMODELING WITH THE ACE-INHIBITOR CAPTOPRIL.

DEGREE FOR WHICH THESIS WAS PRESENTED: MASTER OF SCIENCE, EXPERIMENTAL MEDICINE

YEAR THIS DEGREE GRANTED: 1991

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Date: July 23, 1991

ACKNOWLEDGEMENTS

This thesis would not have been possible without the help of several people.

I am infinitely grateful to my supervisor, Professor Bodh I. Jugdutt who not only sponsored my fellowship from the Alberta Heritage Foundation for Medical Research in 1985, but allowed me to work on this project. In addition, throughout the last several years, he has offered suggestions, advice, scientific guidance and constant encouragement apart from allowing me free access to all resources necessary for this study. More important, he allowed me the freedom to pursue training for my career for a certified academic cardiologist while completing this thesis.

I am also grateful to my co-supervisors, Professor J. R. Burton and Professor K. J. Hutchison for their guidance and encouragement.

I am also indebted to the following of Dr. Jugdutt's staff for their assistance: 1) Emilia Vitelar for typing; 2) Patricia Penner and Claudette Denis-South with echocardiograms; 3) Marie Riesel and John Henriksen with the chronic canine model; 4) Blaine Blinston with computing, statistical analysis and figures.

Finally, I am indebted to my wife Magda and son Bogdan Jr. for spiritual support as well as to the many friends for encouragement.

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June 16, 1991

ABSTRACT

Healing after acute myocardial infarction (MI) is associated with left ventricular (LV) remodeling. To determine whether the chronic reduction of preload and afterload with the angiotensin-converting-enzyme (ACE) inhibitor captopril might prevent LV remodeling and improve LV function, 30 chronically instrumented dogs with similar MI produced by left anterior descending coronary artery ligation were randomized 2 days later to therapy with oral placebo (bd) or captopril (50 mg bd) for 6 weeks. Topographic and functional parameters were measured serially over 6 weeks by two-dimensional (2-D) echocardiography and computer-aided analysis. The main parameters were: expansion index (infarct/non-infarct containing segment length); thinning ratio (infarct/normal wall thickness); regional LV asynergy (akinesis and/or dyskinesis); and LV ejection fraction. Scar size (computerized planimetry) and occluded bed size (postmortem coronary arteriography) were measured at 6 weeks.

Final serial data over 6 weeks were obtained in 20 dogs (10 placebo; 10 captopril). Comparing the captopril and placebo groups, the decrease in mean arterial pressure ($p<0.01$) and mean left atrial pressure ($p<0.01$) between 2 days and 6 weeks were greater with captopril. Heart rate did not differ in the two groups. Infarct scar mass and transmurality were similar in the two groups at 6 weeks. However, scars with captopril showed less thinning ($p<0.001$) and expansion ($p<0.001$) than placebo. Serial echocardiograms showed similar expansion and thinning in the two groups at 2 days. However, between 2 days and 6 weeks, expansion index decreased with captopril ($p<0.001$) but increased with placebo ($p<0.001$). Also, thinning ratio between 2 days and 6 weeks decreased with placebo

($p<0.001$) but did not change with captopril (p=NS). Total LV asynergy was similar in the two groups at 2 days but decreased more by 6 weeks with captopril ($p<0.01$). Global LV ejection fraction was also similar in the two groups at 2 days but showed a greater percent increase with captopril by 6 weeks ($p<0.05$). These changes were associated with increased plasma renin activity and decreased aldosterone level in the captopril group. These results indicate that captopril therapy during healing after acute canine MI over 6 weeks attenuates LV remodeling, that is reduces infarct expansion and thinning, and improves regional and global LV function.

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ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
2-D	Two-dimensional
ECG	Electrocardiogram
I.U.	International units
Kg	Kilogram
LAD	Left anterior descending coronary artery
LV	Left ventricular
mg	Milligram
MI	Myocardial infarction
ng	Nanogram
NO	Nitric oxide
NTG	Nitroglycerin
OHP	Hydroxyproline
pmol	Picomole
L	Liter

1. INTRODUCTION

Infarct expansion is an important, recently recognized early complication of acute myocardial infarction (MI) which contributes significantly to morbidity and mortality after MI (1). It was first described in autopsied human hearts with transmural acute MI as "acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis" by Hutchins and Bulkley (1). In that study (1), infarct expansion was present in 59% of the studied hearts. In contrast, infarct extension, another early complication defined as new myocardial necrosis, was present in only 17% of the studied hearts (1). Two-dimensional (2-D) echocardiography enabled the detection and study of infarct expansion in vivo. Clinical studies (2-4) using this non-invasive technique demonstrated that infarct expansion is responsible for the clinical syndrome of recurrent chest pain, hypotension and heart failure after acute MI (2). In addition, clinical studies indicate that infarct expansion causes significant early mortality (2), and is a major cause of left ventricular (LV) dilatation and impaired functional status (3,4) after AMI. Pathologic and clinical studies have indicated that severe infarct expansion is predictive of cardiac rupture (5), free wall rupture as well as ventricular septal rupture (6). Experimental studies in dog (7) and rat (8) models showed that expansion occurs in transmural infarcts of a critical size, starts early, and progresses over a period of days (8). Early infarct expansion also appeared to play a major role in late aneurysm formation in the rat model (9). These clinical, pathologic, and experimental findings have provided the rationale for recent efforts to use therapeutic interventions after an acute MI to diminish infarct expansion and its sequelae. The pathophysiologic basis

for the use of interventions to modify infarct expansion will be discussed further.

2. REVIEW OF BACKGROUND LITERATURE

2.1. Pathophysiology of Infarct Expansion

The concept of infarct expansion, as a separate pathophysiologic entity from infarct extension (defined as necrosis of additional normal myocardium around the area of the original infarction), was first developed by Hutchins and Bulkley in 1978 (1). These investigators (1) studied 76 consecutive patients who died within 30 days of an acute MI for clinical and morphologic evidence of infarct extension. It was found that the second significant acute and fatal clinical event that occurs in the early days after acute MI can be caused not only by an extension of the infarct (which is the usually assumed clinical diagnosis) but also by previously unsuspected infarct expansion, which is a different pathophysiologic process. Furthermore, they found that infarct extension was infrequent as a cause of death after the second event, being found in only 17% of the infarcted hearts. Expansion, on the other hand, defined as acute dilatation and thinning of the area of infarction, rather than new necrosis, accounted for most clinically diagnosed 'extensions', and was found in 59% of infarcts. In 18% of patients with clinically diagnosed extension (new pain, ST-segment elevation, rise in serum CK level, and increased congestive heart failure), autopsy showed extension alone in 14%, both extension and expansion in 65%, and expansion alone in 21%.

There were five other pertinent findings from the study by Hutchins and Bulkley (1) that need emphasis:

1.) Marked infarct expansion usually developed after 5 days of acute MI and was greater with transmural infarction and first

infarction.

2.) The degree of thinning was greater with marked expansion, more with transmural than subendocardial infarcts, and more with large than small infarcts. Thinning often approached 50% decrease in wall thickness within a week after acute MI.

3.) Expansion of the infarct was associated with an increase in the percent of the LV occupied by necrotic myocardium, LV cavity dilatation and distortion of LV topography. Expansion was explained by stretching and thinning of the infarct with "disruption of necrotic muscle cells where acute inflammatory cells are disintegrating" rather than reparative processes and removal of necrotic cells that are slight or absent at that stage. Expansion thus represents a form of 'intramural myocardial rupture' with thinning and stretching rather than transmural perforation.

4.) An increase in congestive heart failure was the most frequent clinical finding at the time of the second acute event in the patients with infarct expansion, followed by ECG changes, chest pain and hypotension and serum enzyme changes. These manifestations could be related to a combination of mechanical and pathologic processes associated with expansion. Thus, the chest pain could be produced by acute stretching of the ventricular wall, the congestive cardiac failure and hypotension by acute ventricular dilatation, ECG changes by the expanded infarct area projecting to a greater number of precordial leads, and possibly new necrosis secondary to adverse pathophysiologic consequences of acute ventricular dilatation. Tearing of necrotic myocardium during expansion might also lead to accelerated release of enzymes

into the circulation, reflected in a secondary peak of serum CK level.

5.) There was a correlation between the degree of infarct expansion and frequency of clinical infarct extension or the second clinical event. Thus, 70% of their patients with marked expansion had a second clinical event, but only 38% with moderate expansion and none with slight expansion had history of such an event. Although expansion is frequent, occurring in 72% of transmural infarcts, many cases were not suggested by a discrete clinical event. Importantly, of patients without expansion at autopsy, only 6% had a second clinical event.

2.2. Role of Echocardiography in Diagnosis of Infarct Expansion

A diagnosis of LV aneurysm by 2-D echocardiography was first reported in 1976 by Weyman and co-workers (10). In 1977, a computer-aided contouring system for quantifying regional wall motion and thickening on short-axis 2-D echocardiographic images was described by Garrison and colleagues (11). In 1979, Eaton and associates first detected infarct expansion using 2-D echocardiography during the first 2 weeks after acute MI (2). In that study, Eaton and co-workers used the computer-aided semi-automated contouring system of Garrison (11) to measure end-diastolic segment lengths and wall thickness of anterior and posterior LV walls in short-axis 2-D echocardiographic views at the level of papillary muscle tips. Eight of the 28 patients in that study (11) showed evidence of infarct expansion between initial and final studies with disproportionate dilatation and thinning in the infarct zones compared with normal zones. Infarct thinning and increase in total LV circumference were greater among "expanders" than "nonexpanders". The infarcted segment length increased by 48% (range,

26% - 108%) among expanders, remaining unchanged in nonexpanders. Patients with infarct expansion had dramatically higher eight-week mortality than nonexpanders (50% vs 0). Deterioration in functional class during hospitalization was higher among expanders. The development of expansion in infarct segments correlated with the degree of thinning in these areas. The authors concluded that acute regional dilatation is an early severe complication of transmural infarcts and an important mechanism for cardiac dilatation after acute MI.

Subsequent clinical studies using 2-D echocardiography confirmed the importance of early alteration of ventricular topography by infarct expansion. Erlebacher et al (3) defined expansion as an anterior segment length, between 10 to 21 days after an acute MI, greater than 11 cm (the upper limit of normal in controls at the papillary muscle level on 2-D echocardiography). Using this criterion they studied patients using serial 2-D echocardiography over a 3 to 30 month period and found that infarct expansion appearing within 3 weeks of transmural MI was the main contributor to LV dilatation and impaired functional status (3). In addition, they found that significant ventricular dilatation attributable to expansion predicted chronic progressive ventricular enlargement (3). In another study (4), the same group of investigators showed that LV dilatation during the first 3 days after acute MI was mainly caused by dilatation of the infarcted segment rather than the normal uninfarcted segment.

Several other investigators have attempted to quantify LV aneurysms using long axis 2-D echocardiographic views (12-14). Matsumoto and co-workers (14) observed LV aneurysm formation in 44% of patients who had serial 2-D echocardiography between 1 and 28 days after acute MI and found heart failure to be more frequent in patients with

large than small aneurysms.

Regional shape distortion and infarct expansion after acute MI were first quantified on short-axis end-diastolic and end-systolic 2-D echocardiographic images in the recent studies of Jugdutt and co-workers (15-17). Regional shape distortion associated with LV asynergy was characterized in endocardial outlines of short-axis 2-D echocardiographic images from 38 patients with acute MI and 9 healthy individuals by means of both the traditional shape index and new shape distortion indexes (15). The traditional shape index, $P^2/4\pi A$, using perimeter (P) and area (A), gave similar values for infarct patients and controls. However, the peak (P_k) of the angular distribution and the first four moments (M_1 - M_4) of the distance distribution between the "risk" segments with LV asynergy and the computed "ideal" segment of a circle, detected significant regional shape distortion in infarct patients compared to healthy individuals: peak distortion (P_k), 6.0 versus 0.7 mm, $p < 0.001$; M_1 (average), 3.8 versus 1.0 mm, $p < 0.001$; M_2(variance), 20.0 versus 0 mm^2, $p < 0.025$; M_3 (skewness), -217 versus 0 mm^3, $p < 0.025$; M_4 (kurtosis, a measure of peakedness), 19.6 versus 0 mm^4, $p < 0.005$, for the same end-diastolic contours. These five new indexes were much more sensitive in detecting regional shape distortion than the traditional index. The method enables objective evaluation of changes in regional LV shape distortion in 2-D echocardiographic short-axis images.

In two other studies by Jugdutt and colleagues (16,17), endocardial segment lengths, wall thicknesses, and shape distortion of the infarction segments were measured on 2-D echocardiographic views at papillary muscles level at 2 and 10 days after first transmural acute MI

in 278 and 221 patients, respectively. The average incidence of marked infarct expansion (defined as a syndrome of hypotension, LV failure associated with more than 25% diastolic stretching, and thinning of asynergic infarct segments) among the control groups (who did not receive any intervention to reduce infarct expansion) was between 15% to 22%.

In a recent study by Jugdutt and Michorowski (6), infarct expansion and regional shape distortion were significantly more severe in patients who developed acute ventricular septal rupture as compared to patients with acute MI but no mechanical complications although both groups had similar extent of LV asynergy and similar LV ejection fraction.

2.3. Limitations of 2-D Echocardiographic Imaging for Infarct Expansion

The limitations of 2-D imaging in acute MI have been reviewed previously (18). In most studies of expansion, patients with images that were unsatisfactory for analysis were excluded, which accounted for nearly one third of all patients (2-4,11,14). In studying asynergy and infarct expansion, two pertinent points should be emphasized:

1.) Adequate internal landmarks are necessary for measuring segment lengths and thicknesses in infarct and normal segments.

Short-axis images at the levels of the mitral valve, chordae tendineae and papillary muscles which constitute the best views, might underestimate asynergy and regional dilatation which is localized at the very apex of the left ventricle. Systematic recordings of multiple short-axis views from base to apex and extrapolation of the landmarks from higher cross-sections to the apical section can provide better evaluation of the distorted LV

apex. An alternative solution is to use long-axis 2-D echocardiographic views such as apical four-chamber, apical two-chamber, and parasternal long-axis view, as described by Matsumoto and colleagues (14).

2.) The reproductibility of serial measurements depends critically on the ability to image the same area of the left ventricle on each study.

Although some error is inevitable, it can be minimized by careful attention to (i) transducer position, rotation and angulation, (ii) position of the patient and external anatomic landmarks, and (iii) position of internal anatomic landmarks as changes in heart size and rotation can occur over time in this setting.

Despite these limitations, 2-D echocardiography is a powerful, practical and reliable tool for studying the effect of potential therapies for infarct expansion.

2.4. Determinants of Infarct Expansion

Infarct expansion can be regarded as a physical process that is the end result of the interplay of several factors. These have been recently reviewed (19,20). Three major factors are summarized in Table 1 (20). Of these, mechanical forces are especially important because they can be easily modified by pharmacologic agents. Thus, the area of necrotic myocardium with decreased tensile strength is subjected to the distending forces within the ventricular cavity, the intramural stretching forces from the surrounding healthy myocardium and some restraining force from the pericardium, pericardial fluid, and adjacent extracardiac structures. The above mechanisms have been studied in human models (1,5,16,17,21,22) and in addition they can be modified by

pharmacologic interventions (16,17,22-24).

A. Physical Characteristics of MI (Table 1)

Infarct Transmurality.

Several studies have suggested that small subendocardial infarcts are less prone to expansion than large transmural infarcts (1,5,7,8). Only 2 of 45 infarcts with expansion evaluated at autopsy were subendocardial (1). In an experimental model of coronary ligation and embolization in dogs, infarct expansion was present in 17 of 21 transmural infarcts and in none of 18 nontransmural infarcts (7). This could be explained as the probable result of the subepicardial rim of normal myocardium overlying subendocardial infarcts, providing resistance to distending and stretching forces. This normal epicardial rim may be an effective buttress against dysynergic bulging of necrotic muscle during each systole and possibly prevent intramural stretch and rupture. The extent of transmurality also appears to determine the susceptibility to expansion. In an experimental study in rats, none of the large but only focally transmural infarcts showed evidence of expansion (8). A recent autopsy study suggested that the degree of expansion was less marked in hearts with ventricular hypertrophy (25).

Location of Infarction.

An earlier clinical study suggested that infarct expansion was more common with anterior than posterior infarcts (2). In that study (2), 8 of 19 patients with anterior and arteroseptal infarcts developed expansion, whereas none of 9 patients with posterior transmural infarct developed this complication. Subsequent studies (3,4) selected patients with anterior and arteroseptal infarcts so that the initial findings were not verified. Eaton and Bulkley (7) found similar frequency and degree of infarct expansion in anterior and

posterior infarcts in canine models and explained the difference between human and canine infarctions on the basis of the left circumflex coronary artery supplying larger myocardial bed in the dog compared with humans. More recent studies in patients with acute MI have consistently demonstrated evidence of infarct expansion in both anterior and posterior infarcts (16,17). In a recent human autopsy study (25), a greater degree of expansion was noted in infarcts found in the distribution of the left anterior descending than those found in the distributions of the left circumflex and right coronary arteries. Thus, anterior infarction tends to develop more marked expansion than inferior infarction.

Size of Infarction.

In a canine model of acute MI, some degree of expansion was detected in every transmural infarct exceeding a critical weight of 11% of the total LV weight (7). There was, however, no further relationship between the degree of expansion and infarct size beyond the 11% threshold in the dog. Thus, in infarcts ranging from 15 to 18% of the LV mass, there was a disproportionate increase of the infarct-containing ventricular segment length ranging from 15 to 96% (7). In a rat model, the critical infarct weight for expansion was 17% (8). Although there was a positive correlation between the degree of expansion and infarct size in this model, there was also the wide variability of this relationship. Infarcts as large as 56% of the LV mass did not show any evidence of expansion, while infarcts as small as 28% of the LV mass showed marked expansion. The relatively low coefficient of determination in that study suggests that infarct size per se is not the sole determinant of the degree of expansion.

B. Adequacy of Infarct Healing.

Healing after acute MI in humans takes place over 6 weeks to 6 months, depending on infarct size (26). Histopathologic studies have shown that three important processes occur in sequence during infarct healing (27): acute inflammation mainly in the first week; chronic inflammation in the second week; and collagen deposition from the third week onwards. Infarct expansion occurs in the first few days (1,2) and plays a role in the pathogenesis of subsequent sequelae such as cardiac rupture (5,6), acute LV enlargement (4), chronic progressive LV enlargement (3), and ventricular aneurysm formation (9) over the weeks that follow. Although expansion begins early after acute MI, its extent also progresses over several days, suggesting that it might be possible to apply therapeutic interventions during that time to modify expansion and its sequelae (8).

Administration of some anti-inflammatory agents in acute experimental MI resulted in thinner scars (28-30). Indomethacin (31) and ibuprofen (28), given at 15 minutes and 3 hours, respectively, after coronary artery occlusion in dogs caused marked thinning of infarcts at six weeks, despite the fact that indomethacin increases (32) and ibuprofen decreases (33) infarct size in dogs. Early indomethacin therapy in dogs also caused infarct thinning and expansion at seven days (30).

In a recent study of the delayed effects of early infarct limiting therapies on healing after acute MI in dogs (34), it was shown that early therapy (over the first 6 hours after coronary ligation) with nitroglycerin, prostacyclin, or ibuprofen all reduced infarct size but did not reduce infarct collagen content by one week. More important, both nitroglycerin and prostacyclin reduced infarct expansion while

ibuprofen produced more infarct thinning. Furthermore, nitroglycerin appeared to increase infarct collagen content at seven days. The dose of ibuprofen in that study was comparable to the doses used in treatment of postinfarction pericarditis.

In another study in groups of rats treated with multiple intramuscular doses of ibuprofen (12.5 mg/kg for 1 to 6 days), Cannon and associates (35) did not find a difference in thinning between treated and control groups, although ibuprofen appeared to increase collagen content at 21 days.

Therapy with steroids has also been shown to have detrimental effects in acute MI, causing mummification of infarcted myocardium in rats (36), infarct expansion in dogs (29), scar thinning in rats (37) and delayed healing and ventricular aneurysms in humans (21). The most likely explanations include a retardation of the inflammatory response and more rapid resolution of interstitial edema. Other possible explanations include cellular and biochemical effects on infarct healing.

There are at least three important implications of these findings:

1.) The possible delayed effects of drugs on healing should be considered when instituting therapy in the early phase of acute MI;

2.) Certain drugs might be potentially beneficial during the early phase of healing.

3.) Drugs that promote nutrient flow to the infarct through enhanced collateral circulation or collagen deposition might have a favorable effect on both early and late phases of healing.

C. Mechanical forces.

The main mechanical forces acting on the infarct zone are intracavitary (distension), intramural (pull and stretch), and

extramural (restraint). These forces occur throughout the cardiac cycle. Although the magnitude of the forces might be greater during systole, the duration is greater during diastole. In practical terms, the main components of these forces are afterload (mainly during systole), preload (mainly during diastole), contractility and heart rate. They all result in increased wall stress and wall tension.

Afterload.

Afterload represents the net intracavitary systolic distending force. In one study, history of hypertension was more frequent among patients with than those without infarct expansion **(4)**. In autopsy studies, LV aneurysms were more frequent in patients with a history of hypertension **(38,39)**. However, presence of LV hypertrophy appears to play a protective role against infarct expansion **(25)**.

In a recent, randomized, double-blind clinical trial in 30 patients with transmural acute MI (6 anterior, 24 inferior), nifedipine 120 mg/day was found to reduce infarct expansion between 1 and 10 days. The beneficial effect was thought to be attributable to the decrease in blood pressure and afterload **(22)**.

Preload.

Preload represents the net intracavitary diastolic distending force. Its relevance may differ in transmural and subendocardial infarcts.

In subendocardial infarcts, the epicardial rim of normal myocardium acts as a buttress for the infarct during contraction in systole and partially negates the effect of intracavitary systolic pressure. During diastole, this buttressing effect is absent as the epicardial muscle is relaxed, so that the intracavitary pressure and distending force is unopposed.

In transmural infarcts, the distending force during systole may be more important than that during diastole; however, the duration of the latter is longer so that it might have a significant effect on remodeling.

Chronic captopril therapy for 3 months after coronary artery ligation in the rat model was recently shown to attenuate the LV dilatation, reduction of forward output, and changes in LV stiffness, an effect partly related to decreased preload (23). Recently, enalapril was also found to reverse the early expansion (measured by ultrasonic crystals) between 15 minutes and six hours after left-anterior descending coronary artery ligation in anaesthetized, opened chest dogs (24).

Contractility.

The normal noninfarcted myocardium adjacent to the infarcted segment exerts pull and stretch on the latter both during systole and diastole. In addition, compensatory increase in contractility, wall motion and systolic thickening in the adjacent normal myocardium leads to an increase in the traction on the infarcted segment during systole. It is therefore reasonable to postulate that negative inotropic agents might reduce infarct expansion, whereas positive inotropic agents might increase infarct expansion by their effects on contractility in the early phase of healing.

Heart rate.

Heart rate determines the frequency of systolic and diastolic stresses imposed on the infarcted myocardial segment. Tachycardia might lead to a greater degree of expansion. Furthermore, the slight increase in contractility accompanying tachycardia, referred to as the Treppe effect (40), may also contribute to increased wall stress and expansion. Beneficial effects of beta blockers in acute MI (41) might

therefore be partly related to reduced infarct expansion.

The effect of exercise on infarct expansion is likely due to the combined effects of increased afterload, heart rate and contractility. In a rat model of acute MI, forced exercise during the first 24 hours after coronary artery occlusion produced scar thinning (42), whereas exercise commenced one week after coronary occlusion had a similar deleterious effect but was less dramatic (43).

2.5. Therapeutic Approaches for Reducing Infarct Expansion

Therapeutic interventions which can potentially reduce infarct expansion have been reviewed (20) are listed in Table 2.

Nitroglycerin.

Intravenous nitroglycerin (NTG) has been used in a variety of clinical situations including LV failure and pulmonary edema complicating acute MI (44-54). It was found to be effective in reducing infarct size (49-54). The beneficial effects of NTG on infarct size and myocardial performance could be explained in terms of its pharmacologic effects on systemic and coronary circulation (55). Dilatation of peripheral and central veins (56) results in marked decrease in preload through a pronounced venous pooling effect referred to as "pharmacologic phlebotomy". Afterload also becomes reduced by dilatation of systemic peripheral arteries. The net result is a decrease in systolic wall tension, myocardial oxygen consumption and force needed to maintain cardiac output. Dilatation of coronary arteries and collaterals might result in increased blood flow to ischemic regions. The vasodilator properties of NTG are thought to be attributable to a direct effect on vascular smooth muscle cells by denitration of the nitrate ester and oxidation of sulfhydryl groups in vascular receptors (57). It has also been suggested that this

response might also be mediated via a secondary mechanism involving by prostaglandin E (58), or prostacyclin (59,60). It is now recognized that the primary mechanism for NTG action involves metabolic activation to nitric oxide (NO), increase in cyclic guanosine monophosphate (cGMP), modified calcium ion traffic and relaxation (61). Very recently, Palmer et al (62) postulated that endothelium-derived relaxing factor (EDRF) mediates the action of all nitro vasodilators and might be nitric oxide and represent an 'endogenous' NTG.

In therapeutic doses to lower mean arterial pressure by 10% but not below 80 mm Hg, NTG acts predominantly as a venodilator, increasing venous capacity and markedly lowering ventricular filling pressure and preload (55). This effect is associated with dilatation of both pulmonary and systemic veins (63,64). The decreased filling pressures are associated with decreased right and left ventricular volumes (65-67) and a favorable shift in diastolic pressure-volume relations (68). NTG also decreases peripheral vascular resistance, arterial pressure and afterload (69), paralleling the decrease in LV filling pressure (70,71). NTG may increase (69,70), decrease (56), or produce no change (69) in cardiac output. The nonuniform vasodilator response might not only represent different sensitivities of venous or arteriolar smooth muscle to NTG (63) but also of vasoconstrictor reflex adjustments (72). Improved collateral blood flow is a result of combined effects of dilatation of large epicardial coronary arteries (73,74), and intercoronary collateral channels (75,76), reversal of coronary spasm, and increased flow in intramural vessels secondary to decreased subendocardial compression associated with decreased ventricular filling pressure (77).

Intravenous NTG has been shown to improve LV function (45,48)

and myocardial perfusion in acute MI. The decrease in the sum of ST-segment elevation on electrocardiographic precordial ST-segment mapping and perfusion defects on thallium-201 imaging in these patients suggested a decrease in the extent of myocardial ischemia, which supported the findings in studies in dogs (46,75,76,78-79) and humans (47,80,81). NTG infusion also reduced the plasma creatine kinase (CK) enzyme and CK-MB isoenzyme indexes of infarct size (51).

It could be possible that measures to reduce infarct size might ultimately decrease the incidence and the degree of infarct expansion. The effect of early NTG infusion (started within 5.6 hours after onset of symptoms) on the extent of regional LV mechanical dysfunction or asynergy was studied by Jugdutt et al (54) in 22 patients with a first transmural acute MI. Asynergic segments were assessed by serial 2-D echocardiographic recordings. In treated patients, LV function improved as LV filling pressure decreased after NTG infusion. ST-segment elevation on precordial mapping and cumulative CK infarct size indexes were significantly less in the NTG group. There was significant decrease in LV asynergy from pretreatment values by one hour and at 10 days. The pretreatment extent of LV asynergy was similar in control and NTG groups.

It is now recognized that low dose NTG infusion can be given safely during acute MI (55,82). In one large pilot randomized study by Jugdutt et al (16), in which intravenous NTG therapy was used for infarct limitation during the first 48 hours of acute MI, only 9% of patients developed hypotension, promptly reversed by discontinuing the infusion. In this study, therapy was started either within ten hours (early) or after ten hours (late) of onset of pain. Although more NTG patients before therapy, had persistent pain, LV failure, more

ST-segment elevation and LV asynergy, CK-infarct sizes were similar for NTG and control groups, but less in early than late subgroups after NTG. In-hospital complications and deaths were less in NTG than control groups and other variables paralleled CK data. Greatest benefit from low-dose NTG was seen in 1.) the early subgroup, 2.) those with mean arterial pressure greater than 80 mm Hg, and 3.) those with more than 30% improvement in the sum of ST-segment elevations (ΣST), LV asynergy and ejection fraction during early stages of therapy, regardless of infarct location. The frequency of infarct expansion was less in the NTG group than in controls (2% versus 11%).

In the final large randomized study by Jugdutt et al (82), low dose NTG infusion was administered to 154 patients with acute transmural myocardial infarction (156 control patients received 5% dextrose infusion). NTG infusion was titrated to lower mean blood pressure by 10% in normotensive and 30% in hypertensive patients, but not below 80 mm Hg and was maintained for a mean of 39 hours. Creatine kinase infarct size, LV asynergy, LV ejection fraction, expansion index and thinning ratio on serial 2-D echocardiograms were measured. Compared to controls, creatine kinase infarct size was less in treated group both in anterior and inferior infarcts and less in early than late NTG groups (< 4 hours versus > 4 hours after onset of pain). Other indexes of infarct size also improved with NTG compared to controls. Expansion index increased by 31% and thinning ratio decreased by 17% in controls by 10 days but both remained unchanged in the NTG group. Infarct-related complications (infarct expansion syndrome, LV thrombus, cardiogenic shock and infarct extension) were all less frequent in the NTG treated group, as was mortality in-hospital (14% versus 26%), at 3 month (16% versus 28%), and at 12 months (21% versus 31%) The decrease in

mortality was more marked in the anterior subgroup with Q wave and more expansion.

Nifedipine.

The beneficial effect of nifedipine, a calcium channel blocking drug on infarct expansion (22) was mainly caused by decreased afterload. This drug might be especially useful for prolonged therapy after acute MI, as drug tolerance, a potential problem with NTG, is unlikely to occur.

2.6. Role of angiotensin converting enzyme inhibitors (ACE-I) in limitation of infarct expansion and remodeling, and prolongation of survival after myocardial infarction.

Acute MI evokes multiple neuroendocine changes including activation of the renin-angiotensin-aldosterone system (83-86). Elevated plasma renin levels and serum aldosterone were found in patients with acute MI complicated by cardiogenic shock, heart failure and ventricular arrthythmias (84). High plasma renin activity (83,85) and angiotensin II concentrations (85) were observed in AMI with left ventricular failure until 10 days after acute phase. Angiotensin II by its vasoconstrictor effect may reduce coronary collateral flow. In addition, large doses of angiotensin II can produce multifocal myocardial necrosis in rabbits, similar lesions have been found in patients with high circulating leves of angiotensin II before death (87). Peripheral vasoconstriction produced by angiotensin II increases myocardial oxygen demand and may increase infarct size. During the healing phase of infarction increase in the afterload causes infarct expansion (88). The role of increased afterload in infarct expansion is further evidenced by the fact that history of hypertension was more frequent among patients with expansion than those without

infarct expansion (4). Increased levels of plasma aldosterone can cause sodium and water retention, an important factor in precipitating cardiac failure. Administration of aldosterone to dogs with experimental coronary occlusion has been shown to induce ventricular arrhythmias most likely through changes in sodium-potassium ratio in the ischemic myocardium (89). The extent of myocardial necrosis and the level of afterload will determine whether the process of infarct healing will result in contraction of the scar and reduction of the effective infarct size, or in infarct expansion and ventricular dilatation (90).

Interventions with ACE-I after acute MI date back to 1981. Administration of a single dose of oral captopril (25 mg) to patients with acute left ventricular failure complicating acute MI produced a significant fall in pulmonary wedge pressure and systemic vascular resistance and increase in cardiac output (83). Captopril appeared to be a potent vasodilator with effect on preload and afterload which improved cardiac function in acute left ventricular failure complicating acute MI. In an experimental setting, acute coronary artery occlusion in dogs produced increase in plasma renin activity and peripheral vascular resistance and reduction of cardiac output (91). The intravenous ACE-I teprotide, followed by oral captopril, significantly decreased peripheral vascular resistance and mean aortic pressure and increased cardiac output. Clinical observations of beneficial hemodynamic effects of captopril in acute left ventricular failure complicating acute MI were confirmed and extended by other groups (92-94). Anecdotal reports suggest that captopril might be effective in cardiogenic shock complicating acute MI (95). There is an experimental evidence that captopril reduces myocardial infarct size, and that this effect might be mediated by increased collateral flow to

the ischemic zone and reduced afterload (96). These observations were not confirmed by a different group using a conscious dog model (97). Captopril was shown to reduce malignant ventricular arrhythmias after experimental MI in pigs, probably by preventing arrhymogenic effects of angiotensin II (98). ACE-I can also protect rat myocardium during ischemia and reperfusion (99).

The effect of ACE-I on infarct expansion and remodeling was studied in the rat myocardial infarction model. Captopril was selected as the agent with a balanced preload and afterload reducing action and administered to rats for 3 months following coronary artery ligation (23). In the untreated group, left ventricular end-diastolic pressure progressively rose, paralleling infarct size. In the captopril-treated rats, LV end-diastolic pressure remained within normal limits, except in animals with extensive infarcts (> 45% of the LV surface). Mean arterial pressure and total peripheral resistance were reduced and stroke volume and cardiac output were maintained in animals treated with captopril. Left ventricular volumes of the treated rats were significantly less than those of the untreated rats. Administration of captopril ameliorated the reduction in forward cardiac output in all but those rats with extensive infarcts. In addition, LV chamber stiffness which is inversely proportional to infarct size, was normalized by chronic captopril therapy. This same therapy reduced LV dilatation and improved performance in rats with chronic myocardial infarction.

In the rat model, infarction survival has been shown to be inversely related to the size of infarction. The effect of captopril on survival was studied in this model (100). The treated group was given captopril for a year, starting at 14 days after the production of myocardial infarction. The one year survival of the treated animals was

significantly higher than that of control animals, and was most marked with infarcts of moderate size (48% vs 21%). Enalapril, another ACE-I also prolonged survival of rats with experimental MI, with a median 50% survival of 164 days compared to 84 days of untreated animals (101).

Captopril started 3 weeks after coronary artery ligation in rats and continued for 3 months reduced LV mass, LV end-diastolic pressure, mean arterial pressure and total peripheral resistance and maintained cardiac output and heart rate (102). It also reduced end-diastolic volume of LV with moderate infarcts increasing the ejection fraction index. Beneficial hemodynamic effects of captopril after experimental MI were superior to effects of hydralazine (103). In addition to afterload reduction, captopril produced venodilatation and decreased blood volume.

In preliminary reports from this laboratory, we showed that captopril started at 2 days after coronary artery ligation and collateral obliteration (in chronically instrumented dogs) and continued for 6 weeks, reduced expansion index by 30% and prevented late thinning (104). Beneficial effects on LV topography and function were also observed with enalapril in this experimental model (105).

Sharpe et al (106) were the first to report beneficial effects of long-term treatment with captopril after MI in humans. Patients with LV ejection fraction below 45%, but without clinical symptoms of heart failure were started 1 week after MI on captopril (25 mg t.i.d.), frusemide or placebo. Left ventricular volumes were measured serially for up to 12 months with 2-D echocardiography. Captopril-treated patients did not show any change in LV end-diastolic volume index and did show improvement in LV end-systolic volume index, stroke volume index and ejection fraction from 1 month onwards. These beneficial

effects were not observed in 2 other studied groups.

In a study of Pfeffer et al (107) published 5 months after Sharpe's paper (106), captopril was administered to patients with a first MI and a LV ejection fraction $\leq$ 45% on the initial radionuclide study. Treatment was commenced 11 to 31 days after infarction and continued for 1 year. Cardiac catheterization was performed at the commencement and termination of the study. Increase in LV end-diastolic volume was observed in placebo group and was attenuated by captopril which also decreased LV filling pressures. In a subgroup of patients with persistent occlusion of the left anterior descending coronary artery, captopril prevented further ventricular dilatation. Treated patients also had increased exercise capacity. The latter observation was confirmed by another study from the same group (108).

The question of effect of captopril therapy on survival of patients without overt heart failure after acute MI is being investigated in the SAVE (Survival And Ventricular Enlargement) study. This joint USA-Canada trial was begun in 1988 and planned to enroll more than two thousand patients with an LV ejection fraction < 40% randomized between 3 and 16 days after infarction to captopril and placebo and followed for a median of 3 years. The study will provide important information on the long term effects of ACE-I on LV function and survival after MI.

3. PURPOSE OF THE STUDY

The purpose of the study was to determine whether prolonged treatment with captopril, an angiotensin-I converting enzyme inhibitor (Figure 1), can prevent further infarct expansion and late thinning during healing after myocardial infarction in the canine model.

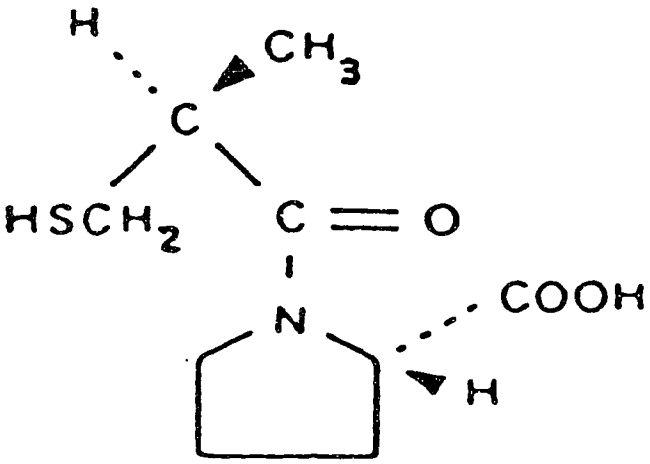
The postulated beneficial effect might be achieved by preload and afterload reduction by captopril.

Since ventricular enlargement and remodeling start early after acute myocardial infarction it was decided to start treatment at 2 days, earlier than in other studies.

The QUESTION can be stated as follows:

CAN REDUCTION OF PRELOAD AND AFTERLOAD
BY PROLONGED CAPTOPRIL THERAPY,
A KININASE AND ANGIOTESTIN I - CONVERTING ENZYME INHIBITOR,
PREVENT FURTHER INFARCT EXPANSION AND
LATE THINNING DURING HEALING AFTER MYOCARDIAL INFARCTION
IN THE CANINE MODEL?

CAPTOPRIL



1-[(S2)-3-mercapto- 2-methylpropionyl]-L-proline [MW 217.29]

A SPECIFIC COMPETITIVE INHIBITOR OF ANGIOTENSIN I-CONVERTING ENZYME (ACE), THE ENZYME RESPONSIBLE FOR THE CONVERSION OF ANGIOTENSIN I TO ANGIOTENSIN II.

ACE IS IDENTICAL TO "BRADYKININASE," AND MAY INTERFERE SIGNIFICANTLY WITH THE DEGRADATION OF THE VASODEPRESSOR PEPTIDE, BRADYKININ.

Figure 1

Legend to **Figure 1.**

The captopril molecule.

4. METHODS AND PROCEDURES

4.1. Experimental preparation.

These have been described in detail previously (109). Healthy mongrel dogs of either sex, weighing 18 to 22 kg were anesthetized with sodium pentobarbital (30 mg/kg i.v.) and ventilated throughout the instrumentation procedures with room air through a cuffed endotracheal tube. A limited left lateral thoracotomy was performed and the heart suspended in the pericardial cradle. Plastic catheters were placed in the external jugular vein, right common carotid artery, and left atrial appendage. The ends of the catheters were exteriorized through a subcutaneous tunnel between shoulder blades for future hemodynamic recordings. The catheters were primed with heparinized saline to maintain patency. Pairs of metal epicardial beads were sutured in the mid left ventricular plane for consistent 2-D echocardiographic images for analysis of regional LV topography and function.

The mid left anterior descending coronary artery was ligated permanently distal to the first diagonal branch with 2 sets of silk sutures. The presence of ischemia was visually confirmed by the presence of a cyanotic area distal to the ligation and ST-segment elevation recorded on the epicardial surface electrogram. The chest was carefully closed in layers. Penicillin (1×10^6 I.U.) and streptomycin (1g) were given intramusculary after surgery. Instrumentation and chest closure took an average of 60 minutes (range, 50-70 min). Dogs were returned to animal area and allowed to recover.

4.2 Protocol.

This is summarized in **Figure 2**. Forty-eight hours after coronary artery ligation, thirty surviving healthy dogs were randomized to oral therapy with either daily captopril (50 mg b.i.d., n=15) or

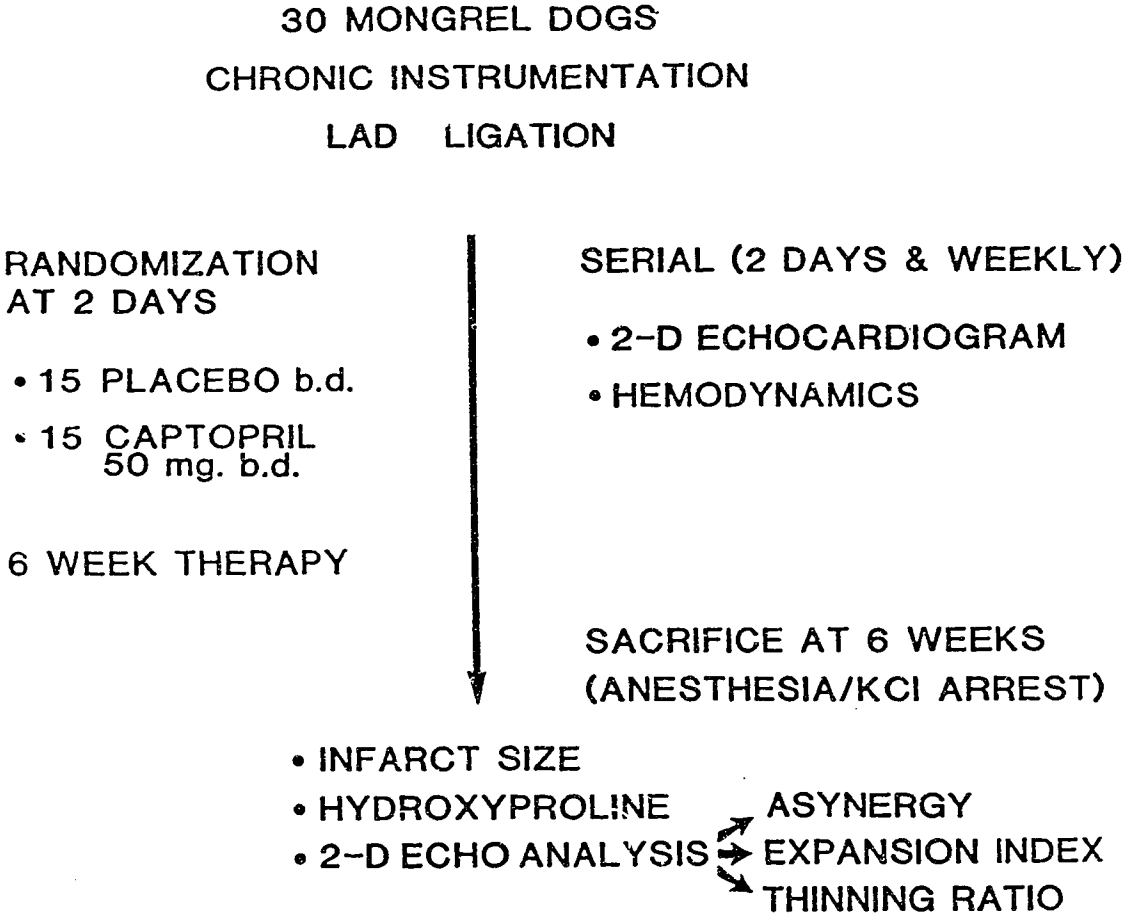

30 MONGREL DOGS
CHRONIC INSTRUMENTATION
LAD LIGATION
RANDOMIZATION
AT 2 DAYS
• 15 PLACEBO b.d.
• 15 CAPTOPRIL
50 mg. b.d.
6 WEEK THERAPY
SERIAL (2 DAYS & WEEKLY)
• 2-D ECHOCARDIOGRAM
• HEMODYNAMICS
SACRIFICE AT 6 WEEKS
(ANESTHESIA/KCl ARREST)
• INFARCT SIZE
• HYDROXYPROLINE
• 2-D ECHO ANALYSIS
ASYNERGY
EXPANSION INDEX
THINNING RATIO

Figure 2

Legend to **Figure 2.**

Schematic of the experimental protocol.

2-D, two-dimensional; ECHO, echocardiogram; KCl, potassium chloride; LAD, left anterior descending coronary artery.

placebo (b.i.d., n=15) orally and both were continued for 6 weeks.

The dogs were fed regular dog food and allowed free access to fluids. No attempt was made to treat heart failure by fluid restriction or pharmacotherapy.

4.3. Serial hemodynamics, electrocardiograms and 2-D echocardiograms.

Serial recordings were performed at 2 days and weekly up to six weeks in dogs under mild sodium pentobarbital sedation (20 mg/kg i.v.). Hemodynamic measurements were obtained via fluid filled catheters and pressure transducers (Statham P23Db) with the dogs standing in the sling. Electrocardiograms (ECG) were recorded on a Gould pen recorder. Lead II of the ECG was also recorded with echocardiograms. 2-D echocardiographic recordings were obtained with a Diasonics V3400R phased array ultrasonograph with a dog lying on its right side. Blood samples were taken for monitoring blood gases, hemograms, and electrolytes. Venous plasma renin and aldosterone levels were measured in selected dogs by radioimmunoassay (94).

4.4. Measurement of occluded bed size and infarct size (109,110).

At 6 weeks, dogs were again anesthetized and the chest opened. Diastolic cardiac arrest was produced with an overdose of intravenous potassium chloride. The hearts were excised, washed in normal saline and weighed. Postmortem coronary arteriography was performed on the fresh hearts to define the anatomic boundaries of the occluded bed. The injected heart was packed with gauze to preserve diastolic proportions and fixed in 10% buffered formalin for 48 hours.

Five equally spaced transverse sections (1 to 1.5 cm thick) were cut from the level of the coronary occlusion to the apex and section radiographs were taken (**Figure 3**). This allows the definition of the anatomic risk region, that is the area supplied by the occluded artery

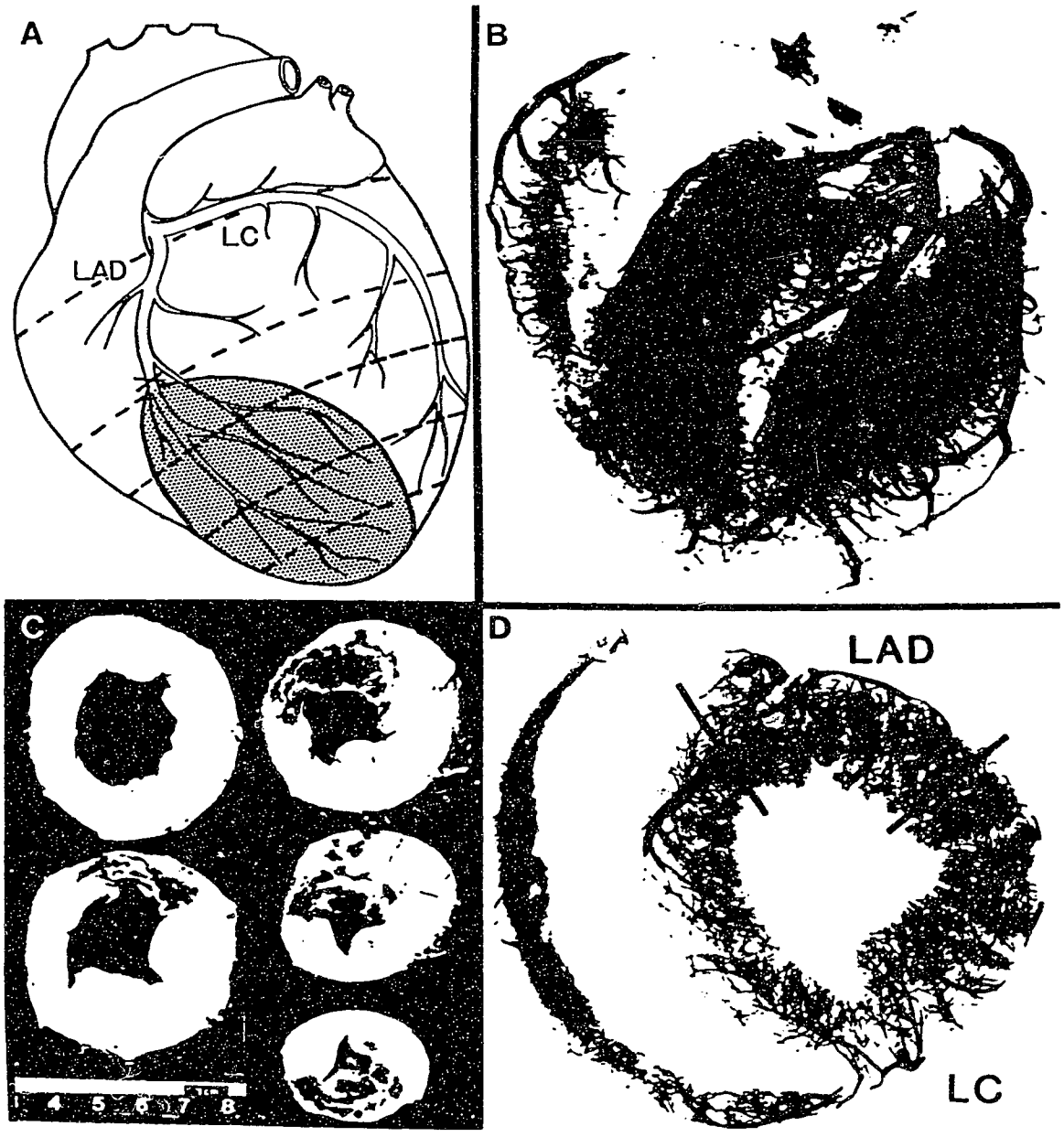


Figure 3

Legend to **Figure 3.**

Postmortem coronary arteriograms and radiograms for occluded bed size.

A. Schematic showing method of ligation of the mid left anterior descending coronary artery **(LAD)**, the occluded bed (stippled) and transverse sections (broken line). **LC**, left circumflex coronary artery.

B. Radiograph of a postmortem arteriogram. Epicardial and transmural vessels are visualized.

C. Transverse sections of left ventricular rings. The infarcted anterior wall is clearly seen in rings from base to apex. The right ventricle has been removed.

D. Radiograph of a transverse section with markings (solid black lines) of the occluded beds across the wall.

as a watershed between the intramural interdigitating branches of the left anterior descending and left circumflex coronary artery (32). The LV transverse sections were then weighed after removing the right ventricle, fatty and valvular tissue, large epicardial vessels, fibrous connections and pericardial adhesions. Outlines of the LV rings and infarcts were then made on plastic overlays and markings of occluded beds (risk regions) copied from section radiographs, using computerized planimetry (HP 9835A and digitizer HP 9874A) (Figure 4). Areas of infarct, occluded bed and non-infarcted myocardium were computed. Total infarct and occluded bed masses were computed for each heart by summing values for each ring.

Histology and morphometric analysis was done on a 5 mm slice from the middle of the occluded bed as described previously (111). Triplicate sections (5 μm) were stained with hematoxylin and eosin, Mallory's stain, or Masson's trichrome, respectively, and examined for infarction and collagen.

4.5. Determinations of total hydroxyproline content (111).

Transmural myocardial tissue samples (Figure 5) were taken from the central zone of the infarct or occluded bed and the center of the nonoccluded bed (111). Samples were weighed (100 to 200 mg), freeze-dried to constant dry weight (12 hours), reweighed and hydrolyzed in 6N hydrochloric acid at 125 degrees centigrade for 3 hours and 200 psi pressure in an autoclave. Instead of neutralization and decoloration, 1 ml aliquots of the acid hydrolysate were evaporated, washed with 1 ml water and redried in the same tubes as described by Bergman and Loxley (112). Hydroxyproline content, as a marker for collagen, was measured on a spectrophotometer (Unican SP-1800), using the method of Neuman and Logan (113) as modified by Martin and Axelrod

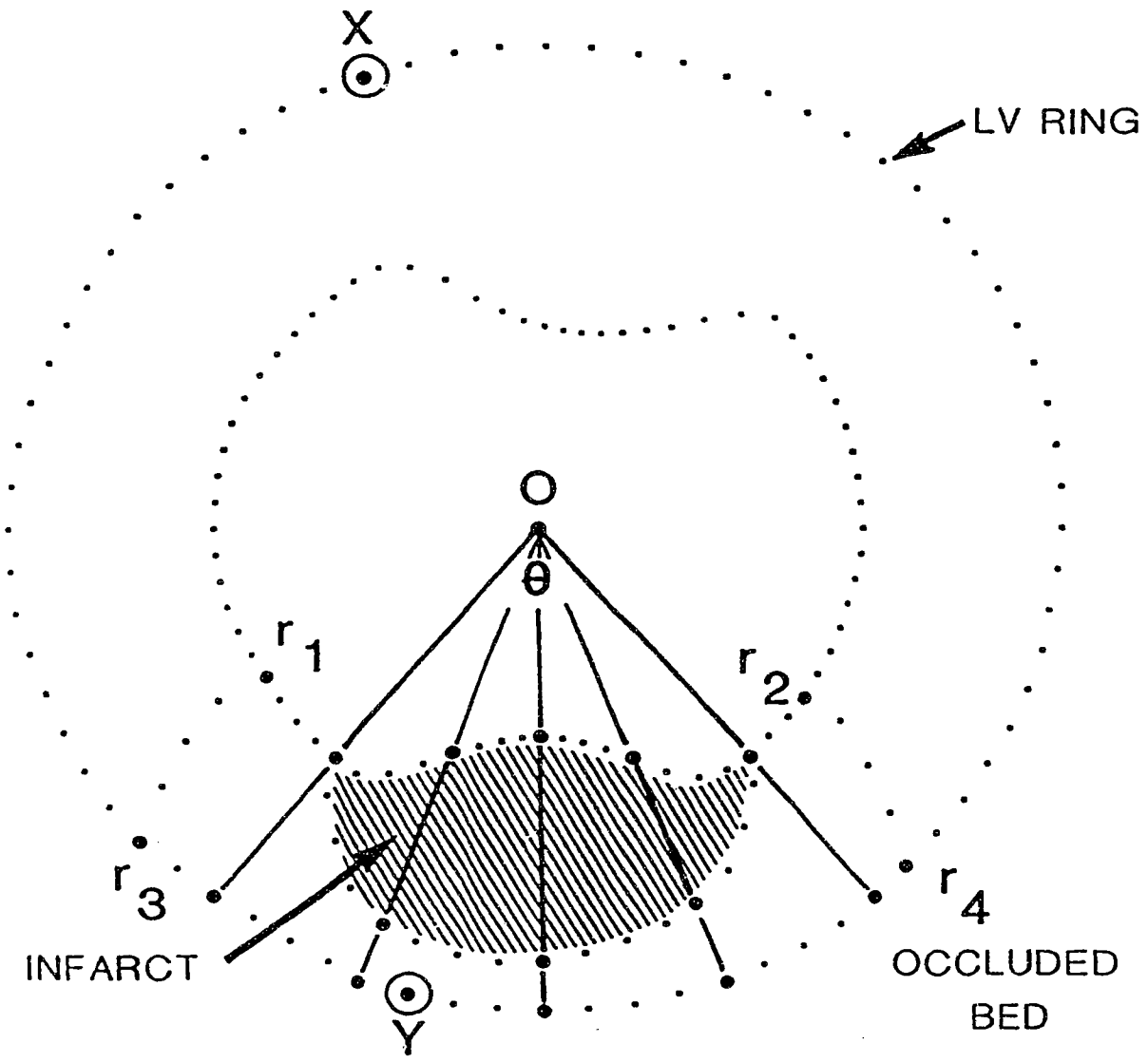


Figure 4

Legend to Figure 4.

Ccmputerized planimetry for mapping infarcts, risk regions and left ventricular rings.

Map of the infarct, occluded bed, and left ventricular (LV) section generated by computerized planimetry. Points along inner and outer contours are at 5 degree intervals. The center O of the inner contour represents the computed zero moment of inner perimeter. Radii were constructed at intersections of the inner contour with the infarct and extended to the outer contour so that measurements could be made of the angular extent of the infarct (θ) and distances along selected radii ($\theta/4$ apart) and along circumferences between appropriate pairs of points in the wall (large dots). Between the extreme radials, the average infarct wall thickness was computed. The average normal wall thickness was computed from similar measurements between radials mirrored on the opposite normal wall. Intersections of the boundaries of the occluded bed with the inner and outer contours (r_1-r_4) and the right ventricle with the outer LV contour (X,Y) were also recorded. **Modified from Jugdutt, BI, Circulation 1985; 72:907-914 (With Permission).**

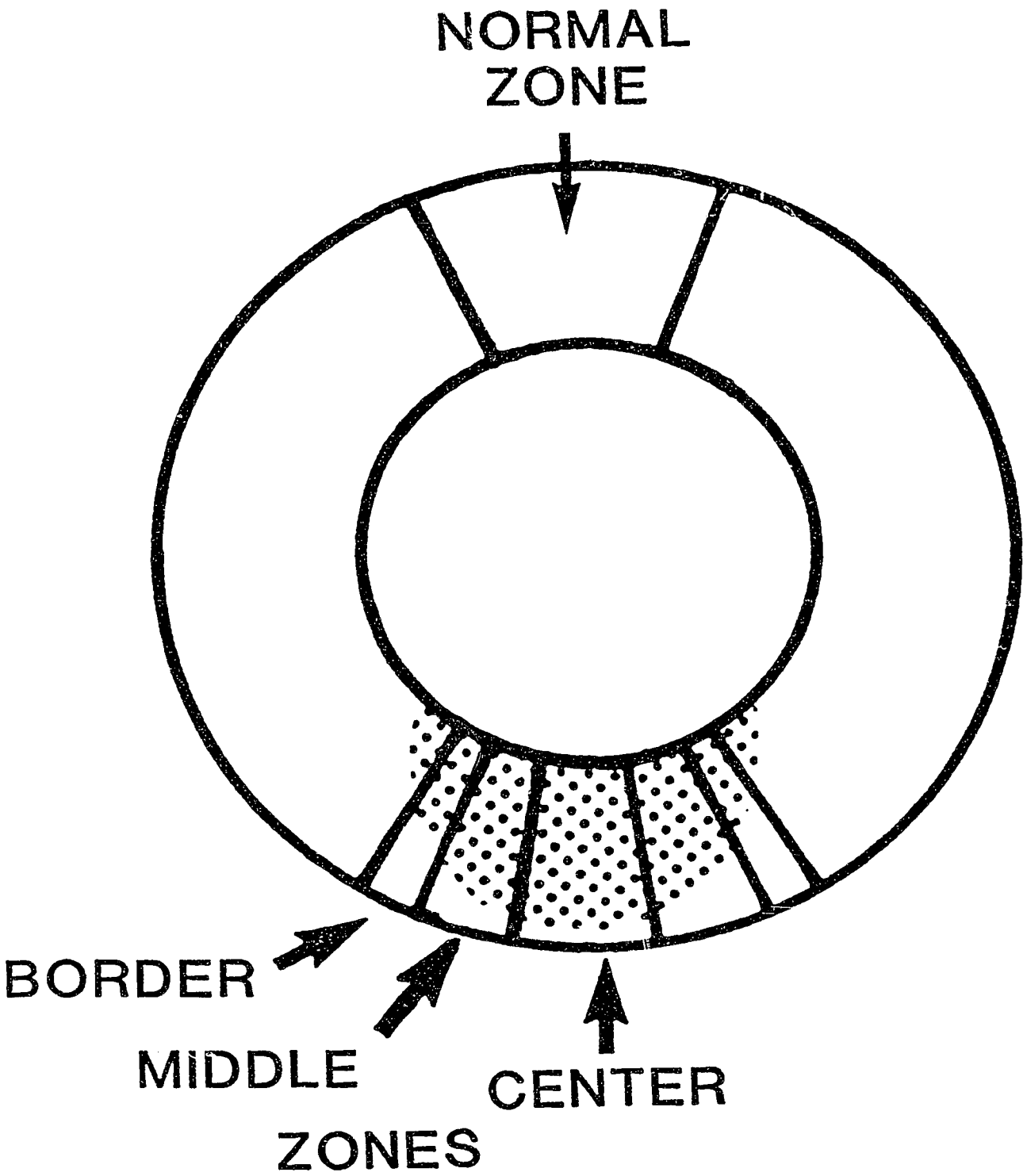


Figure 5

Legend to **Figure** 5.

Method of sampling for hydroxyproline.

Transmural wall samples were taken from border, middle and center zones of the infarct (stippled) and the normal zone. The visually normal epicardial rims were removed from the transmural samples before the assay. **Modified from Jugdutt, BI, Circulation 1985; 72:907-914 (With Permission).**

(114), and expressed in mg/g dry tissue weight.

4.6. **Serial 2-D echocardiographic recordings (115,116).**

The 2-D echocardiographic recordings were obtained with a Diasonics V3400R phased array ultrasonograph with the dog lying on its right side **(115,116)**. The images were excellent **(Figure 6)** and enabled visualization of all LV walls in the five parasternal short axis views (from base to apex at mitral, chordal, mid papillary and low papillary and apical levels), the parasternal long-axis view and apical four-chamber and two-chamber views. In all cases, the position of the dogs and transducers were noted for use in serial studies. Images were video-taped for review in real time, slow motion and single frame formats. Echocardiograms were coded (tape and log number) and were analyzed in a blinded fashion, independently by two observers (B.L.S-M and B.I.Jugdutt). Intra-and inter-observer error for all parameters were less than 5%, within the reported range **(115,116)**. Endocardial and epicardial LV outlines were traced on plastic overlays from ECG-gated images at end-diastole and end-systole. Markings of the extent of LV asynergy defined as akinesis or dyskinesis (no systolic inward motion or systolic outward motion and lack of systolic thickening or systolic thinning) were made on each short axis LV endocardial diastolic outline in real time. It was verified that the asynergic segment did not show systolic inward endocardial motion and thickening by comparing wall thicknesses in systole and diastole (Varian, light-pen system) and comparing aligned diastolic and systolic outlines. Asynergic segments in the endocardial diastolic outlines were digitized (HP 9874A) for computing the circumferential extents of asynergy in each short axis view (expressed as percent) and the total extent of LV asynergy (as percent surface area of the endocardial shell), using the apical

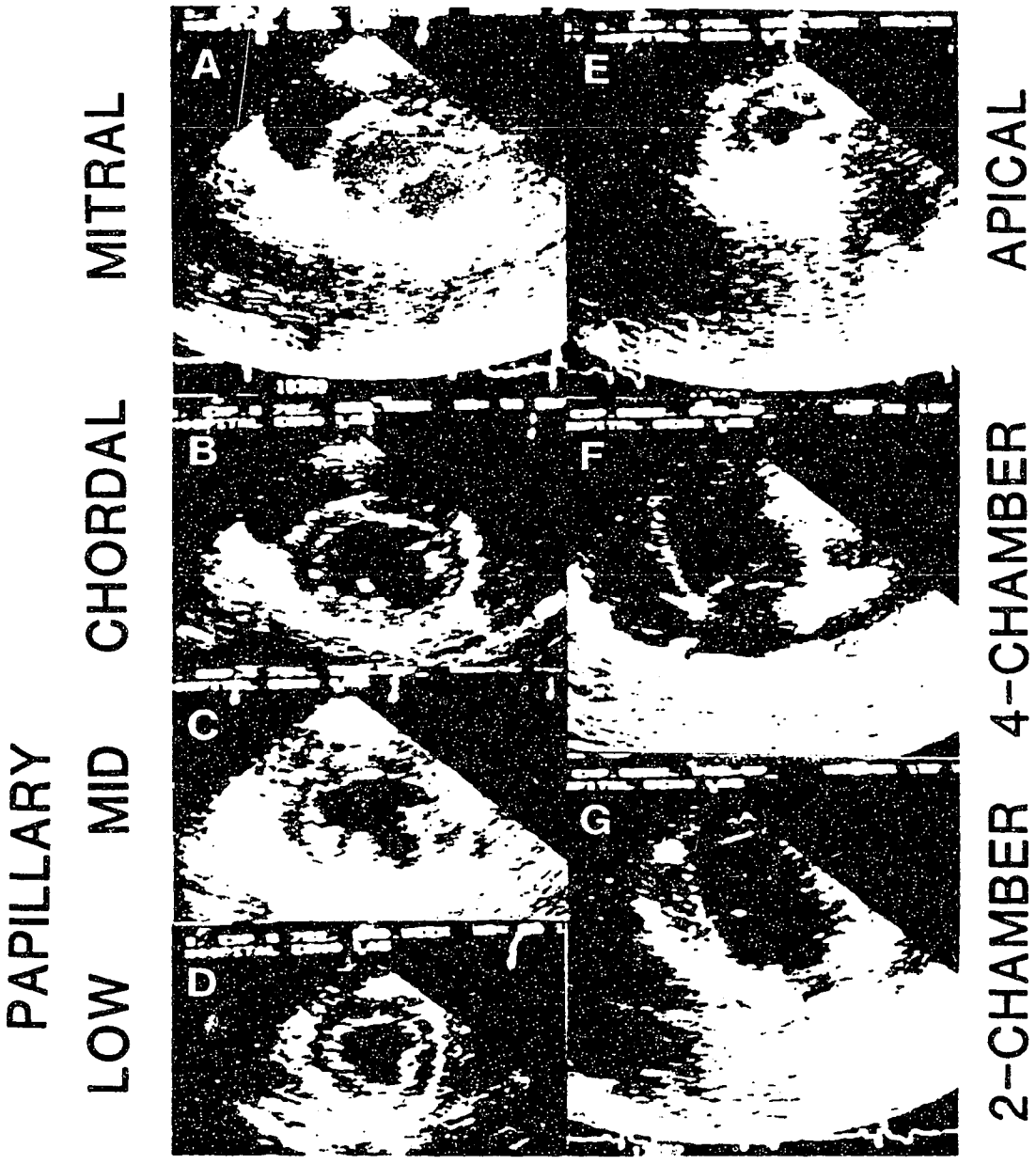

PAPILLARY
LOW
MID
CHORDAL
MITRAL
A
B
C
D
E
F
G
2-CHAMBER
4-CHAMBER
APICAL

Figure 6

Legend to **Figure 6.**

Typical echocardiographic images for analysis.

Short-axis images at five levels **(A to E)** and apical long-axis images from **(F and G)** were used systematically for analysis of left ventricular topography and function.

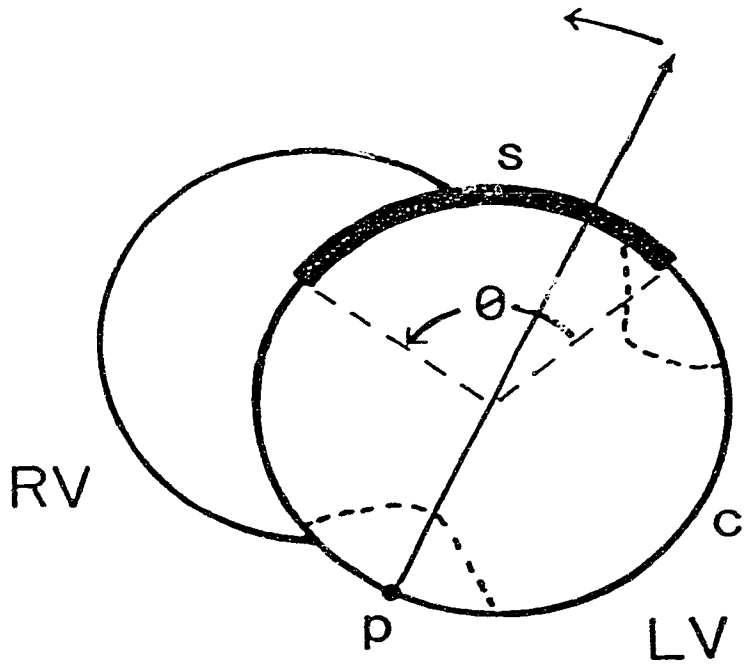
four-chamber and 3-5 serial short axis views (**Figure 7**). Global LV ejection fractions were derived from end-diastolic and end-systolic LV volumes, computed from outlines of short-axis views and two long-axis views (apical four- and two-chamber) using the modified Simpson's rule (**Figure 8**). Ejection fraction was computed as percent of (end-diastolic volume − end-systolic volume)/end-diastolic volume.

Expansion index (**117,119**) was defined as the ratio of the asynergy containing endocardial segment length to the normal segment length (**Figure 9**). The mid point of the base of the papillary muscle formed the landmark for segment lengths. Thinning ratio (**117-119**) was defined as the average thickness of the asynergy containing to the normal wall thickness (**Figure 9**).

4.7. STATISTICS

Data are expressed as means ± standard deviation. The significance of difference within a group was assessed by analysis of variance (ANOVA), between groups by multivariate ANOVA, and among serial measurements with a group by multiple measures ANOVA. Computer programs were run on the Hewlett-Packard 9835A computer and 9874A digitizer interface with a VAX 750 computer. Statistical significance was set at a p value <0.05.

CIRCUMFERENTIAL EXTENT OF LV ASYNERGY
IN SHORT AXIS VIEW



TOTAL SURFACE AREA OF LV ASYNERGY

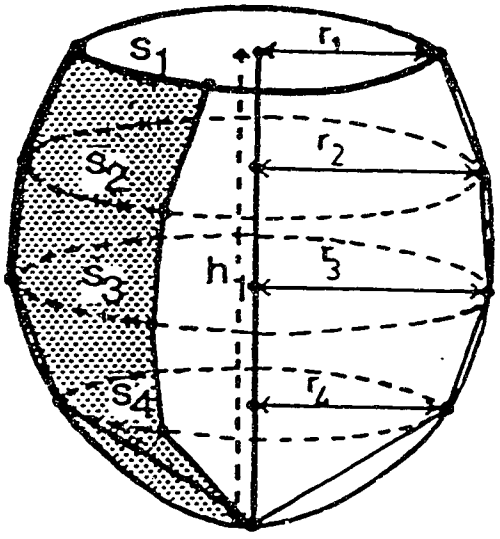


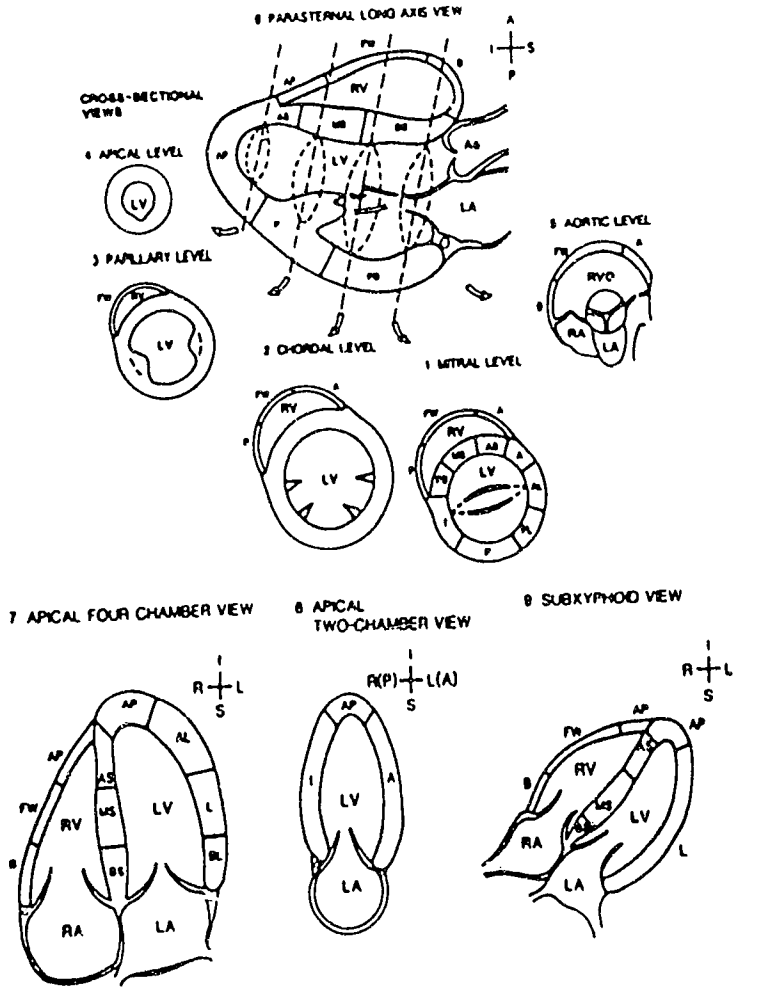
Figure 7

Legend to Figure 7.

Method of computing endocardial surface area of left ventricular asynergy from echocardiograms.

Top. The extent of asynergy (s), marked on end-diastolic outlines of parasternal short-axis images at four serial levels from base to apex on 2-D echocardiography was expressed as percent of circumference (c). A point (p) at the midpoint of mitral, chordal, or papillary muscle landmarks was identified. An axis was constructed from this point to the anterior wall to bisect the area of the left ventricular section. Radial coordinates were defined from the axis and the angular extent (θ) of asynergy measured. Radii (r) were measured from the midpoint of this line. Bottom. Calculation of total left ventricular asynergy, as percent surface area of the endocardial shell constructed from the four short-axis sections and height (h) derived from the left ventricular long-axis length in the apical four-chamber view. The left ventricle is assumed to consist of three frustums of a right circular cone and an apical cone. **Modified from Jugdutt, BI, et al, Circulation 1983; 68:1264-1273 (With Permission).**

A.



mitral

chordal

mid-papillary

low-papillary

B.

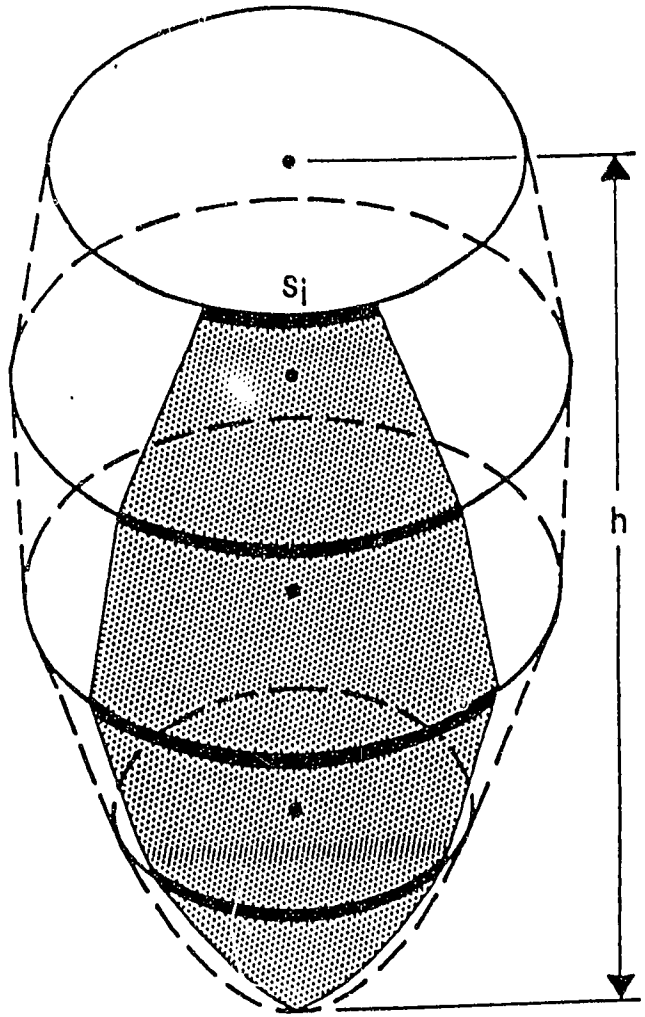


Figure 8

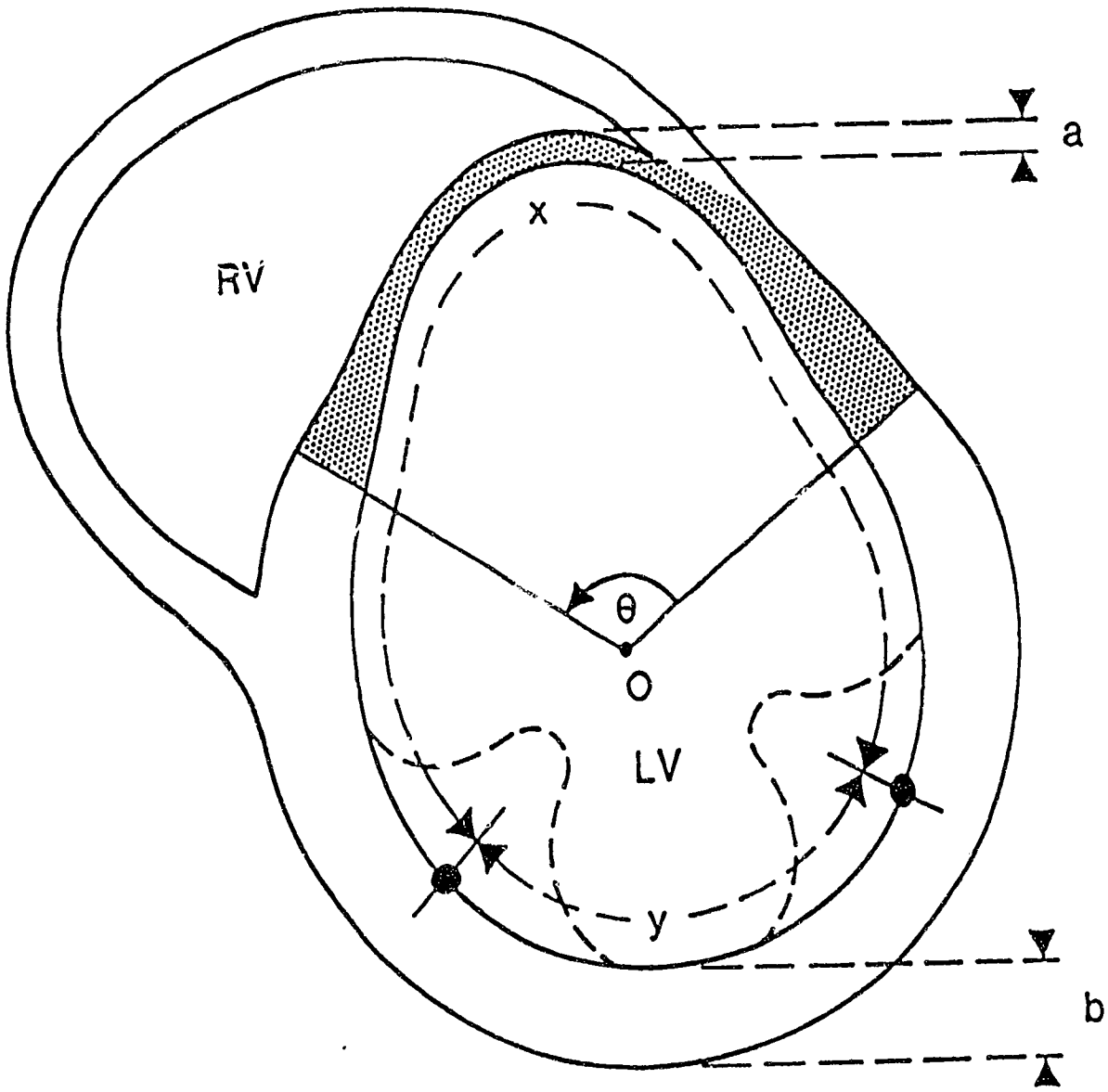
Legend to **Figure 8.**

Method of computing left ventricular volumes from echocardiograms.

A. Systematic topographic echocardiographic images were obtained in the planes shown. Outlines of these images at end-diastole and end-systole were made using a light-pen analysis system.

B. The outlines were combined by 3-dimensional reconstruction using short-axis and long-axis data. **h**, average height of the long-axis. S_i, circumferencial extent of asynergy. The algorithm is based on the modified Simpson's rule, as used previously in this laboratory **(82,117-119)**.

EXPANSION INDEX AND THINNING RATIO



θ = angular extent of asynergy

x = endocardial length of asynergy-containing segment

y = endocardial length of segment without asynergy

a = average thickness of asynergic zone

b = average thickness of non-asynergic zone

EXPANSION INDEX = x/y

THINNING RATIO = a/b

Figure 9

Legend to **Figure 9.**

Method of computing expansion index and thinning ratio.

A mid left ventricular (LV) section at end-diastole from a dog with anterior infarction. Left ventricular segment lengths were measured from the midpoints of papillary muscle landmarks. RV, right ventricle.

5. RESULTS

The characteristics of the 30 dogs that were randomized to the control and captopril groups are summarized in **Tables 3 and 4**, respectively. Five dogs from each group were excluded from final analysis. Five dogs in the control group (#4,7,13,14,15) and four dogs in the captopril group (#20,25,29,30) died or were sacrificed prematurely. One dog in the captopril group had no infarct at 6 weeks (#28). Thus, ten of 15 dogs from each group survived between 2 days and 6 weeks after acute MI. Their data were subjected to detailed analysis and form the basis of this thesis. The 10 dogs that were lost before scheduled sacrifice represent a 33% total loss, which is within the reported range with this chronically instrumented canine model for studying changes in topography and function after acute MI **(115, 116)**.

The data on age, sex, weight and experiment duration for the two groups are shown in **Tables 3 and 4**. The final control (n=10) and captopril (n=10) groups were comparable with respect to age (2.0±1.4 versus 1.9±1.1 years), sex (50% versus 70% males), weight (19.9±2.7 versus 20.8±2.0 Kg), and interval to sacrifice (44±3 versus 44±2 days).

5.1. Hemodynamic changes.

Hemodynamics for control and captopril groups are summarized in **Tables 5,6,7 and 8** and presented graphically in **Figure 10**.

There was no difference in heart rate between the groups over 6 weeks **(Table 5)**. Thus, comparing control and captopril groups, mean heart rates were similar post-operatively or post-ligation (140±26 versus 139±16 beats/min, NS) and at 6 weeks (89±15 versus 91±11 beats/min, NS). The data is presented as percent change between 2 days and 6 weeks in **Figure 10**. There was no difference in the percent change in heart rate in the control group compared to the captopril

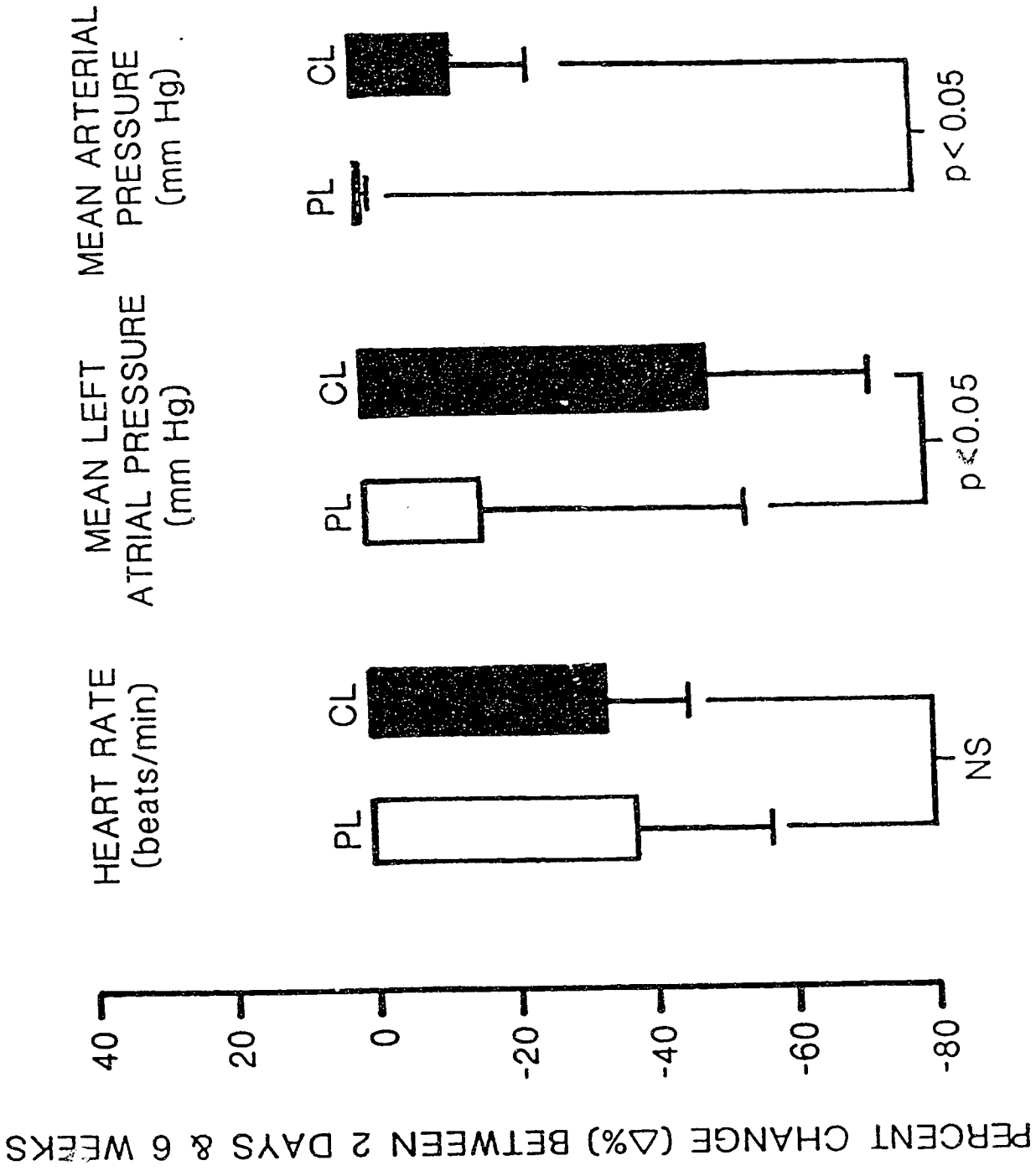

PERCENT CHANGE (Δ%) BETWEEN 2 DAYS & 6 WEEKS
40
20
0
-20
-40
-60
-80
HEART RATE (beats/min)
MEAN LEFT ATRIAL PRESSURE (mm Hg)
MEAN ARTERIAL PRESSURE (mm Hg)
PL
CL
NS
p<0.05
p<0.05
PL = PLACEBO (n=10)
CL = CAPTOPRIL (n=10)

Figure 10

Legend to **Figure 10.**

Hemodynamic changes in captopril (CL) and placebo (PL) groups.

Captopril decreased mean left atrial pressure and mean arterial pressure during healing after canine anterior myocardial infarction.

group (-38±19 versus -34±12%, NS).

In contrast, mean arterial pressure, a measure of LV afterload, fell more between 2 days and 6 weeks in the captopril group than in the control group. Thus, comparing captopril to the control group **(Table 6)**, the mean arterial pressure was less at 2 weeks (101±10 versus 114±16 mm Hg, $p<0.005$) and at 5 weeks (99±9 versus 112±8 mm Hg, $p<0.005$) with captopril. Between 2 days and 6 weeks, there was 13% decrease in mean arterial pressure in the captopril group. In the control group, the percent change in mean arterial pressure was negligible (-0.2 ±0.1 %). The decrease with captopril was therefore significantly different from that in controls (-13±11 versus -0.2±0.1 %, $p<0.01$) **(Figure 10)**. The changes in mean arterial pressure were reflected in changes in both systolic and diastolic pressure. The values for baseline (pre-operative), post-ligation (post-operative) and final (6 weeks) intervals are shown in **Table 7**.

Also in contrast to heart rate changes, mean left atrial pressure, a measure of LV filling pressure or preload, fell significantly more between 2 days and 6 weeks in the captopril group than the control group **(Table 8)**. Thus, comparing captopril and control groups, mean left atrial pressure was less at 1 week (6.5±1.8 versus 12.5±4.6 mm Hg, $p<0.005$) and at 6 weeks (5.8±2.3 versus 9.7±3.6 mm Hg, $p<0.025$) with captopril. The percent decrease **(Figure 10)** in the captopril treated group was significantly greater than in the control group (-50±22 versus -16±38 %, $p<0.01$). Filling pressure, but not blood pressure, remained decreased 24-48 hours off captopril presacrifice.

5.2. Infarct or scar size data

The data on infarct or scar size are summarized in **Tables 9 and 10**, respectively. Comparing the captopril to the control group, mean

LV mass (77±10 versus 65±13 g, $p<0.05$) and occluded bed mass (15±6 versus 11±4 g, $p<0.1$) were slightly greater with captopril than placebo groups, reflecting biologic variation (32). However, there was no statistically significant difference between the captopril and control groups in scar mass (4.5±3.4 versus 4.0±1.5 g, NS), occluded bed size as percent LV (19.9±8.1 versus 16.0±5.4 %, NS), scar size as percent LV (5.8±4.5 versus 6.1±2.2 %, NS) or scar size as percent occluded bed (32.1±23.6 versus 40.2±15.9 %, NS). **Figure 11** summarizes infarct or scar size data in both studied groups. Histopathology showed scar tissue at 6 weeks with variable epicardial rims in both groups.

5.3. Effect of captopril on scar morphology and topography

The sixteen main topographic measurements (111) on the mid-LV region of postmortem hearts for control and captopril treated groups are summarized in **Tables 11 and 12 and 13 and 14**, respectively. The maximal transmural extent of infarct ranged between 85% and 100% (mean 97.0±6.3 %) in the control group and between 41% and 100% (mean 86.1±23.5 %) in the captopril treated group. There was no significant difference in scar transmurality between groups ($p=0.2$ or NS). The infarct to normal wall thickness ratio, or thinning ratio (parameter #8, **Tables 11 and 13**) in the control group was significantly less than in the captopril treated group (0.57±0.12 versus 0.82±0.15, $p<0.001$). This indicates attenuation of thinning of the infarct zone with captopril. Expansion index (parameter #16, **Tables 12 and 14**) was also significantly less in the captopril treated group compared to the control group (2.14±0.35 versus 2.72±0.31, $p<0.001$).

The average computer generated geometric maps from the LV rings of the two groups are shown in **Figure 12**. Although these maps have not been corrected for the slightly larger LV size in the captopril group,

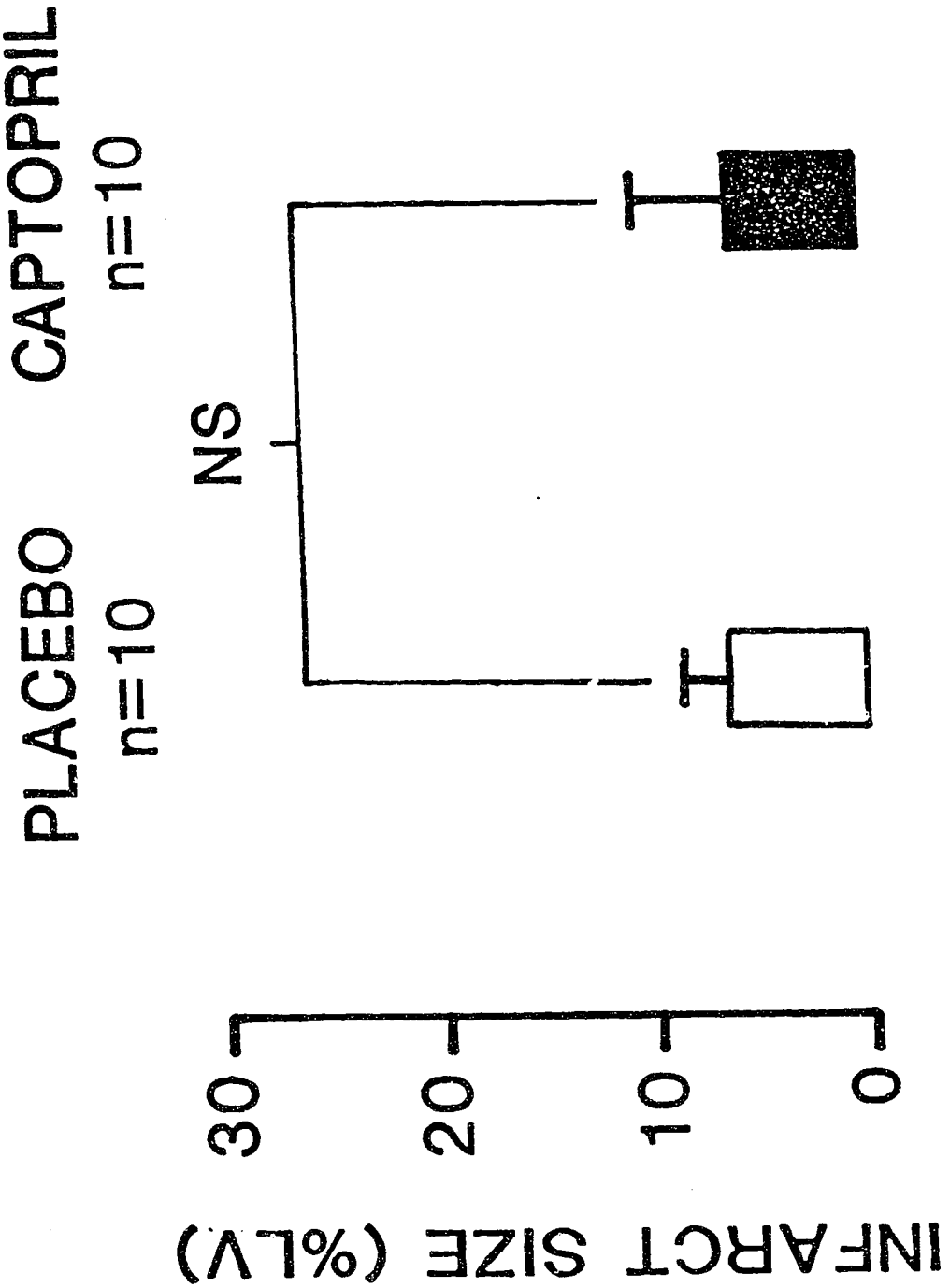


Figure 11

Legend to **Figure 11.**

Effect of captopril on scar size.

The scar sizes, expressed the percent ratio of grams of infarct to grams of left ventricle, were similar in the two groups.

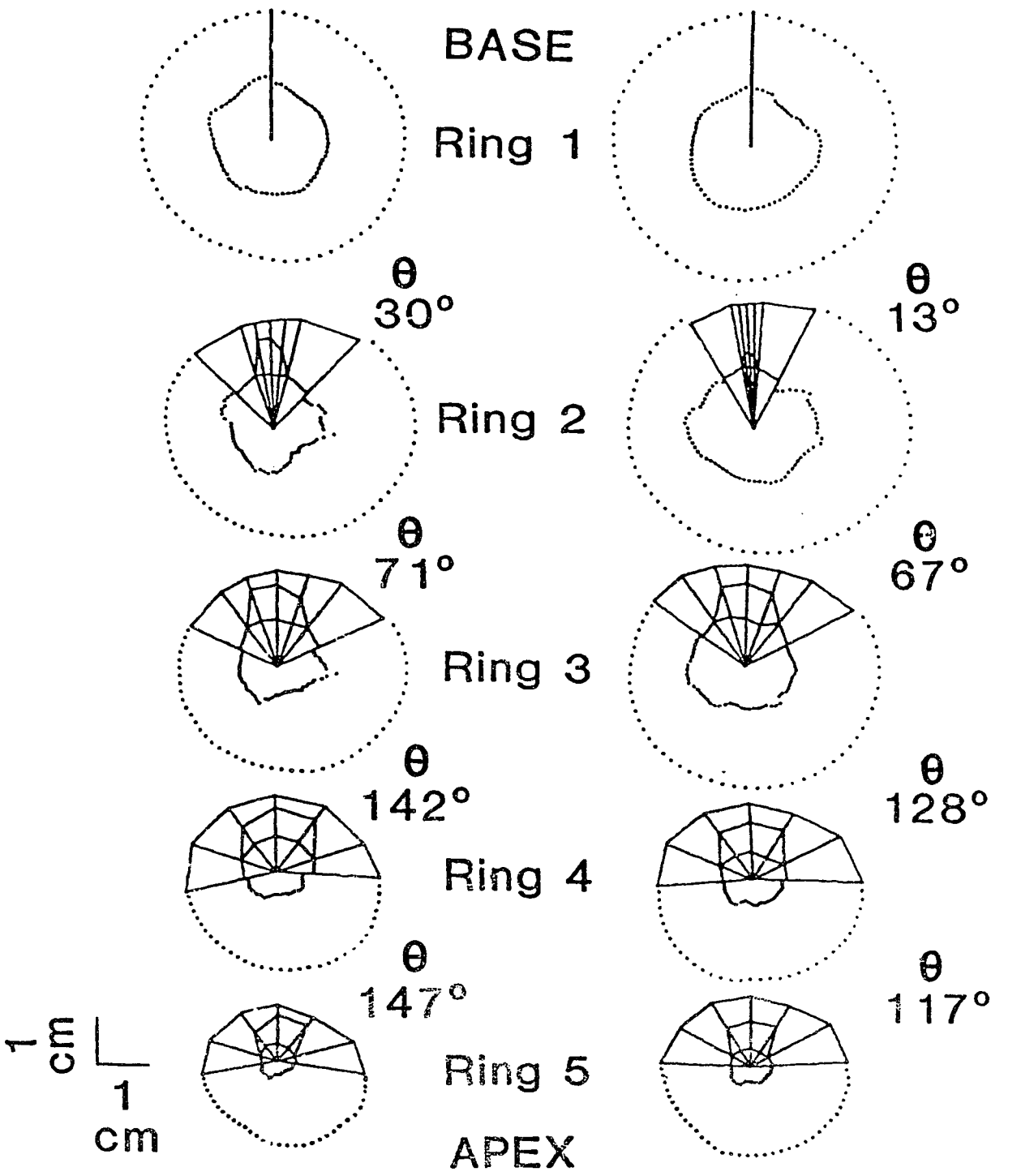

CONTROL (n=10)
CAPTOPRIL (n=10)
BASE
Ring 1
θ 30°
θ 13°
Ring 2
θ 71°
θ 67°
Ring 3
θ 142°
θ 128°
Ring 4
θ 147°
θ 117°
Ring 5
APEX
1 cm
1 cm

Figure 12

Legend to **Figure 12.**

Computerized maps of scar topography.

Computer generated average maps of the left ventricular rings (1 to 5) from base to apex are shown for control and captopril groups. The angular extents of the scar (θ) in degrees are shown and were less with the captopril group compared to the placebo control group. The scars were also thinner with placebo.

the angular extents of the scars were slightly greater in infarcted rings 2 to 5, from the base to the apex, for the control group compared to the captopril group: ring 2, 30±31° versus 13±19°; ring 3, 71±72° versus 67±70°; ring 4, 142±67° versus 128±74° and ring 5, 147±76° versus 117±79°. However, these values did not reach statistical significance ($p>0.05$). Differences in infarcted wall thickness were most marked in the apical region. Thus, the thicknesses of the infarct wall in the captopril and control groups were as follows: ring 2, 1.31±0.11 versus 1.10±0.07, $p<0.001$; ring 3, 1.09±0.08 versus 0.99±0.07, $p<0.005$; ring 4, 1.00±0.10 versus 0.8±0.11, $p<0.001$; ring 5, 1.07±0.11 versus 0.79±0.09, $p<0.001$. These results further support the idea that captopril prevents infarct thinning.

The non-infarct wall thickness in the map **(Figure 12)** was slightly greater (NS) in all regions from base to apex in the captopril compared to the control group. Thus, the normal wall thickness for captopril and control groups from base to apex were: ring 1, 1.49±0.09 versus 1.38±0.07, $p<0.005$; ring 2, 1.47±0.12 versus 1.42±0.07, p=NS; ring 3, 1.43±0.12 versus 1.40±0.11, p=NS; ring 4, 1.48±0.13 versus 1.39±0.04, $p<0.05$; ring 5, 1.37±0.03 versus 1.33±0.06, $p<0.05$. The cavity dimensions were not significantly different between the groups, in part due to artifacts of formalin fixation.

A typical example of the attenuation of post infarct remodeling is shown in **Figure 13.**

5.4. Effect of captopril on changes in topography during infarct healing: 2-D Echocardiographic Data

Serial topographic data derived from 2-D echocardiographic studies are presented in **Tables 15 and 16** for control and captopril treated groups, respectively. The changes in the two main topographic indexes,

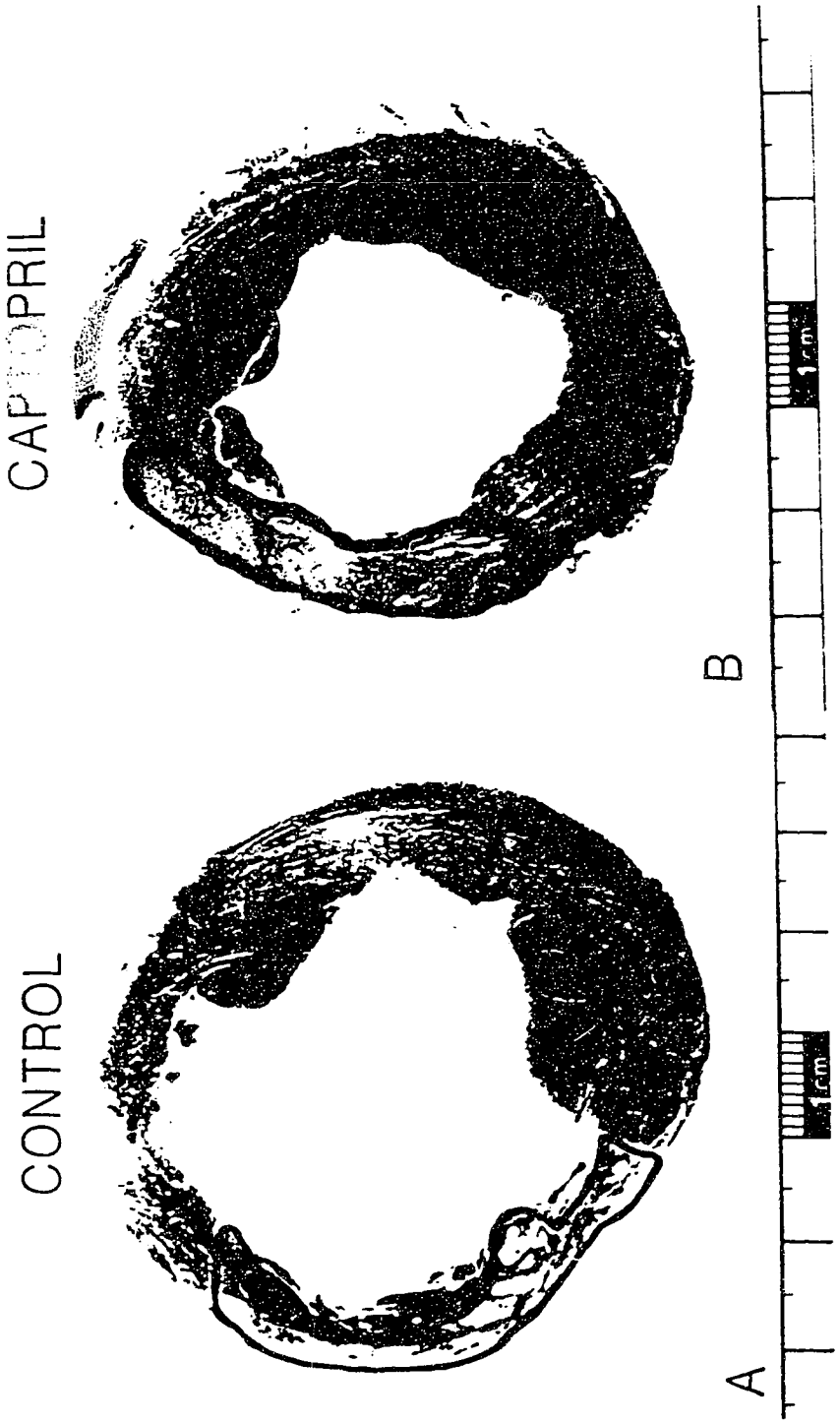


Figure 13

Legend to **Figure 13.**

Illustrative examples of scars in captopril and control groups.

Dramatic remodeling with scar thinning, outward bulging and dilatation is shown in the transverse left ventricular section from a heart in the control group. Equally dramatic attenuation of remodeling is shown in the transverse section from a heart in the captopril-treated group. The borders of the scars are marked. The infarct areas and masses were similar in the two hearts.

namely expansion index and thinning ratio, are also summarized in Figure 14.

Expansion index increased in the control group between 2 days and 6 weeks (2.29±0.25 versus 2.91±0.40, p<0.001) but decreased in the captopril treated group (2.31±0.24 versus 1.82±0.15, p<0.001). There was less expansion in the captopril group than the control group as early as 2 weeks (2.19±0.41 versus 2.61±0.38, p<0.05) and this beneficial effect was even more marked by 6 weeks (1.82±0.15 versus 2.91±0.40, p<0.001).

Thinning ratio decreased significantly in the control group between 2 days and 6 weeks (0.84±0.10 versus 0.63±0.10, p<0.001) but did not change in the captopril treated group (0.83±0.11 versus 0.80±0.05, NS), indicating prevention of further scar thinning with captopril. This difference between the two groups was more marked between 3 and 6 weeks, indicating that captopril prevented the marked late thinning that occurs during infarct healing **(111,115,116)**. Thus, compared the control group, the captopril group had less thinning at 3 weeks (0.81±0.04 versus 0.71±0.13, p<0.01), 4 weeks (0.81±0.07 versus 0.68 ± 0.11, p<0.005), 5 weeks (0.80+0.06 versus 0.66±0.10, p<0.001), and 6 weeks (0.80±0.05 versus 0.63±0.10, p<0.0005).

5.5 Effect of captopril on changes in left ventricular function during infarct healing: 2-D Echocardiographic Data

Serial functional data are presented in **Tables 17 and 18**. The changes in the two main functional indexes, regional endocardial surface area of LV asynergy and global LV ejection fraction are also summarized in **Figure 15**.

Total LV asynergy, an index of regional contractile dysfunction, was comparable in the control and captopril groups at 2 days (12.1±3.0

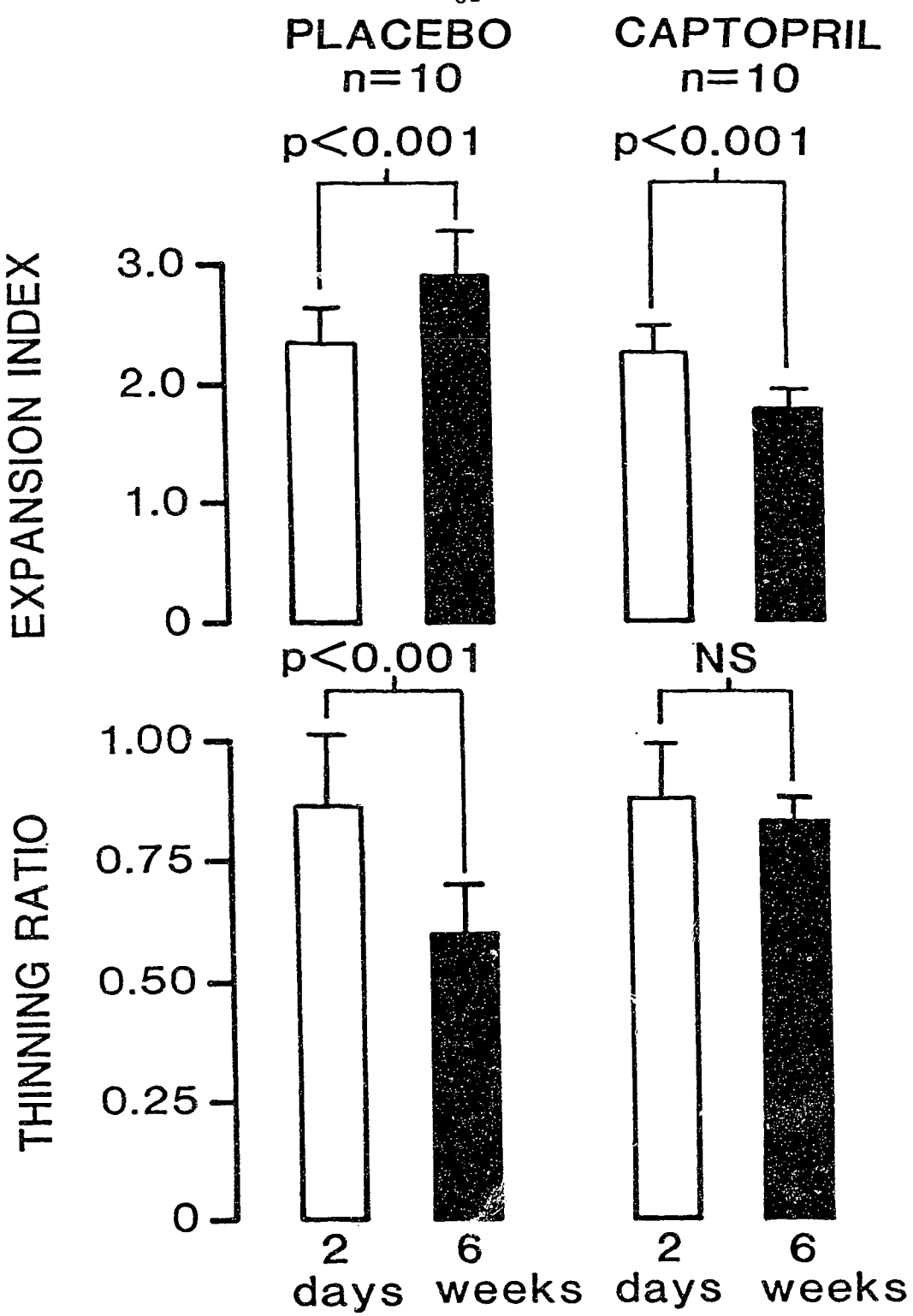

PLACEBO
n=10
CAPTOPRIL
n=10
p<0.001
p<0.001
EXPANSION INDEX
3.0
2.0
1.0
0
p<0.001
NS
THINNING RATIO
1.00
0.75
0.50
0.25
0
2
6
2
6
days
weeks
days
weeks

Figure 14

Legend to **Figure 14.**

Effect of captopril on infarct expansion and thinning during infarct healing.

Bar graphs show expansion and thinning in the placebo group and attenuation of both in the captopril group between 2 days and 6 weeks during healing after acute anterior myocardial infarction.

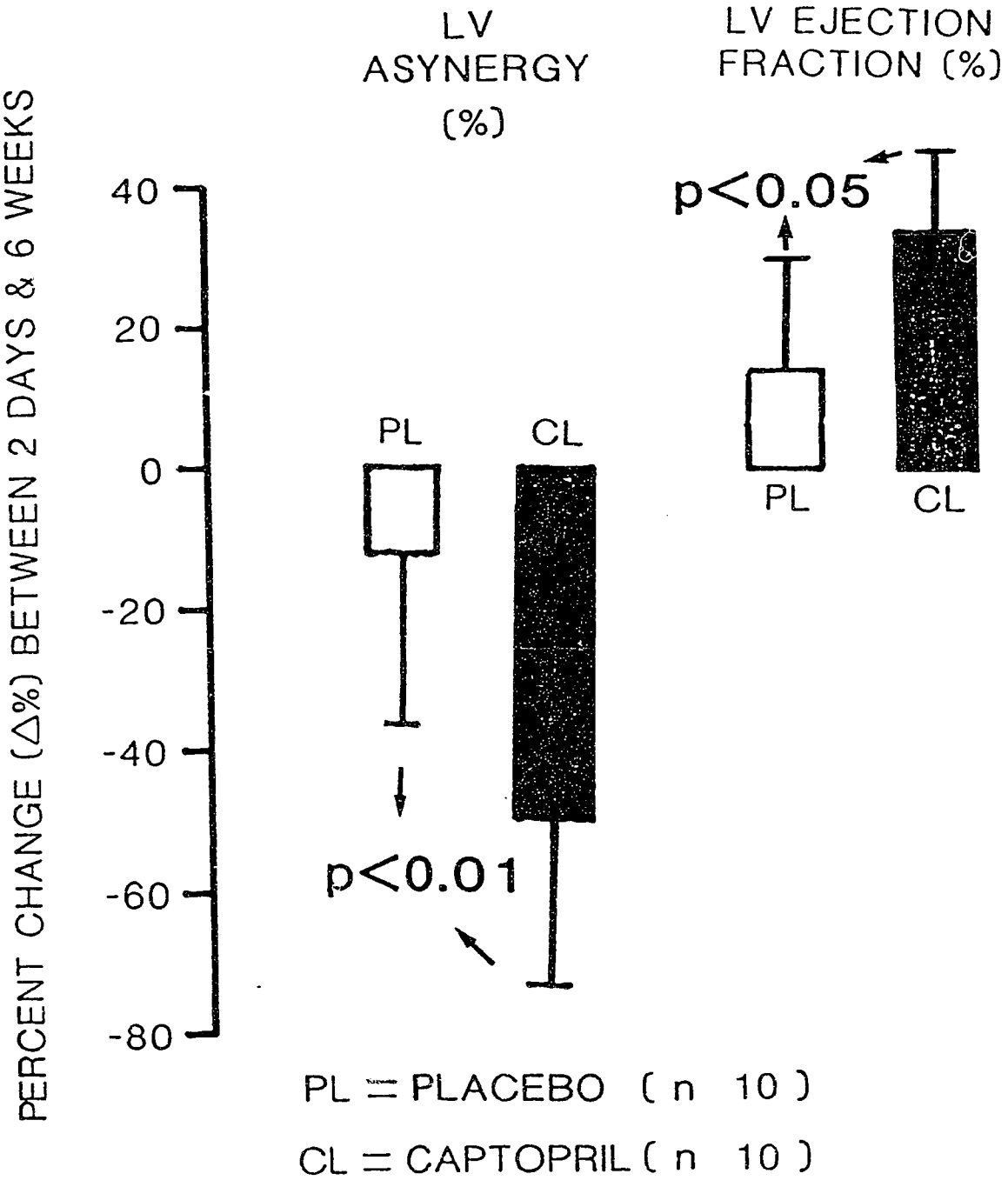

LV ASYNERGY (%)
LV EJECTION FRACTION (%)
PERCENT CHANGE (Δ%) BETWEEN 2 DAYS & 6 WEEKS
40
20
0
-20
-40
-60
-80
PL
CL
p<0.01
p<0.05
PL
CL
PL = PLACEBO (n 10)
CL = CAPTOPRIL (n 10)

Figure 15

Legend to **Figure 15.**

Effect of captopril on left ventricular (LV) function during infarct healing.

The percent decrease in LV asynergy between 2 days and 6 weeks post infarction was greater with captopril than placebo. Also, the percent increase in LV ejection fraction was greater with captopril than placebo.

versus 12.2±4.9 %, NS). In the control group LV asynergy decreased slightly between 2 days and 6 weeks (12.1±3.0 versus 10.8±4.0 %, $p<0.05$). The percent decrease was only 11% over the 6 weeks in the control group. In contrast, the captopril group showed a 48% decrease in LV asynergy over the 6 weeks, from 12.2±4.9 % to 6.4±4.4 % ($p<0.001$). The value at 6 weeks was less in the captopril group than in the control group (6.4±4.4 versus 10.8±4.0%, $p<0.01$). The percent decrease in LV asynergy over the 6 weeks with captopril was greater than in the control group (48% versus 11%, $p<0.01$).

Global LV ejection fraction, an index of global LV systolic contractile function or performance, was similar in the control and captopril groups at 2 days (38.5±5.8 versus 40.2±6.6 %, NS). Ejection fraction improved by 16% between 2 days and 6 weeks in the control group (38.5±5.8 versus 44.6±5.5 %, $p<0.05$). In contrast, ejection fraction improved by 34% over the same interval in the captopril group (53.8±10.4 versus 40.2±6.6%, $p<0.001$). Ejection fraction at 6 weeks was greater in the captopril group than in the control group (53.8±10.4 versus 44.6±5.5 %, $p<0.025$). The percent increase in LV ejection fraction was also greater in the captopril group than the control group (34% versus 16%, $p<0.05$).

5.6. Effect of captopril on scar collagen

Data on transmural myocardial hydroxyproline content, a marker for collagen, in the central zone, the margin zone and the border zone of the infarct scar as well as the normal myocardium for both treatment groups is summarized in **Table 19**. There was a gradient in hydroxyproline across the infarct, with more hydroxyproline in the infarct center than the margin and the border regions. In the control group, the mean hydroxyproline content (in mg/g of dry weight) was 37.44

±7.37 in the central zone, 28.25±9.77 in the margin zone, 13.49±7.43 in the border zone and 5.49±1.53 in the normal myocardium. There was a significant difference between hydroxyproline content in the central zone of the infarct scar and the normal zone ($p < 0.001$). In the captopril treated group, the mean hydroxyproline content was 35.61±12.94 mg/g in the central zone, 23.46±15.02 mg/g in the margin zone, 15.34±8.14 mg/g in the border zone and 5.54±1.09 mg/g in the normal zone. Again there was a significant difference between hydroxyproline content in the central infarct scar zone and normal myocardium ($p<0.001$). However, there was no difference in hydroxyproline content of the corresponding central infarct scar or normal myocardium zones between the control group and the captopril treated group. **Figure 16** summarizes the hydroxyproline contents in the captopril and control groups. Thus, captopril has no significant effect on the collagen content of the infarct scar.

5.7. **Effect of captopril on renin and aldosterone**

The data on venous plasma renin and aldosterone from 5 dogs each in the control and captopril groups are summarized in **Tables 20 and 21.**

Plasma renin activity **(Table 20)** was higher at 6 weeks in the captopril group compared to the control group (7.5±2.9 versus 2.9±1.3 ng/ml/hour, $p<0.025$). There was a marked increase in plasma renin activity between the post-ligation level and 6 weeks (4.1±1.2 versus 7.5±2.9 ng/ml/hour, $p<0.05$) with captopril.

Plasma aldosterone activity **(Table 21)** was significantly less at 6 weeks in the captopril group compared to the control group (14±26 versus 149±100 pmol/L, $p<0.025$). There was a marked decrease in plasma aldosterone activity between the post-ligation level and 6 weeks in the captopril group (510±216 versus 14±26 pmol/L, $p<0.005$).

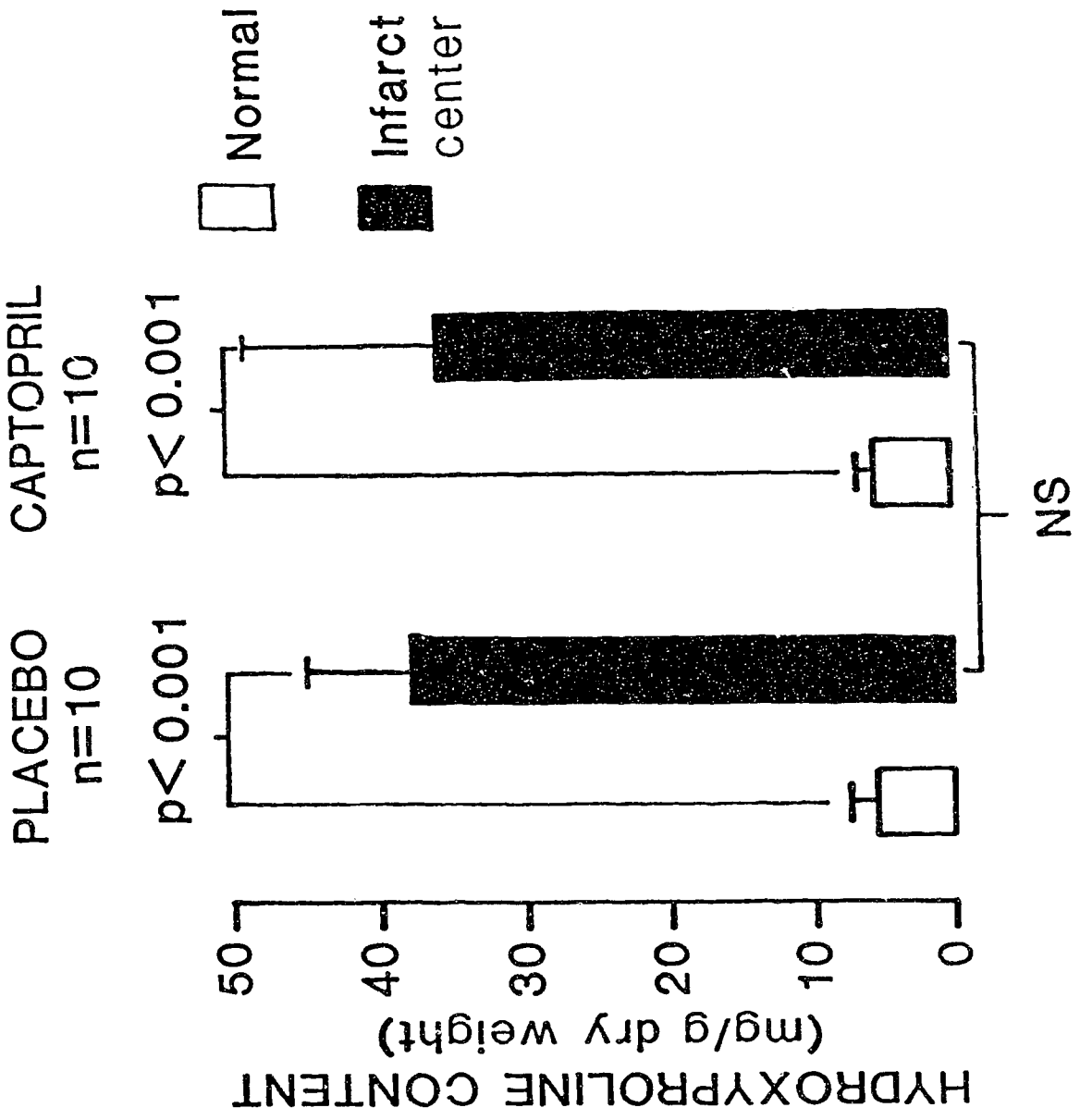

HYDROXYPROLINE CONTENT
(mg/g dry weight)
50
40
30
20
10
0
PLACEBO
n=10
p< 0.001
CAPTOPRIL
n=10
p< 0.001
NS
Normal
Infarct
center

Figure 16

Legend to **Figure 16.**

Effect of captopril on infarct collagen.

There was no difference in hydroxyproline content of scars in the placebo and captopril groups. Infarct hydroxyproline was similarly increased in both groups.

6. DISCUSSION

There were four major findings in this study:

1.) Healing after acute MI in the canine model is associated with LV remodeling which is manifested by early infarct expansion, late thinning and persistent LV dysfunction as shown by serial 2-D echocardiography.

2.) Chronic captopril therapy during healing over 6 weeks after acute canine MI attenuated LV remodeling, manifested by decreased late infarct thinning, marked decrease in early infarct expansion and marked improvement in LV function compared to the placebo group.

3.) These beneficial effects of captopril therapy were associated with a sustained decrease in preload and afterload but no change in heart rate over the 6 weeks, suggesting that the beneficial effects of captopril on LV topography and function were most likely due to the sustained reduction of preload and afterload. The effect of captopril was confirmed by evidence of inhibition of neurohumoral activation.

4.) Infarct hydroxyproline content, which reflects collagen deposition in the infarct zone, was not affected by captopril therapy.

6.1. Healing after myocardial infarction in the dog.

It was shown in the earlier study **(111)** that temporal changes in LV topography occur during healing after myocardial infarction. There was a significant increase in cavity area, endocardial circumference and expansion index (infarct/normal endocardial segment length) by 7 days. By 6 weeks there was a significant decrease in thinning ratio (infarct/normal wall thickness). In addition, between 2 days and 6 weeks there was decrease in the infarct area and increase in the noninfarcted segment length. Over 6 weeks, hydroxyproline content

(which is a marker of collagen) was unchanged in the normal regions of the LV, but increased progressively between 7 days and 6 weeks in infarct zones. Progressive infarct contraction occured over 6 weeks with infarct size at 6 weeks being 40 % less than at 2 days. Thus, healing in canine infarcts is known to be associated with cavity dilatation and infarct expansion within 7 days, followed by infarct contraction and thinning by 6 weeks, and collagen increase between 7 days and 6 weeks. The histopathologic and topographic mapping results in the present study confirmed evidence of expansion and thinning in the infarct zone in the placebo control group and their attenuation in the captopril group.

Also, in this study, temporal changes in LV topography were followed by serial quantitative 2-D echocardiographic studies. Since the 1979 study of Eaton et al (2), who first reported regional cardiac dilatation after acute MI using serial 2-D echocardiography, this technique became a recognized tool to study infarct expansion in vivo. The technique has been refined in this laboratory for accurate quantitation of LV remodeling (6,82,115-119). Since the quality of echocardiographic images in dogs is excellent, this model of myocardial infarction is particularly suitable for utilization of the 2-D echocardiographic technique.

6.2. Effect of captopril on topography and LV function.

Size of infarction is one of the most important major determinants of infarct expansion. In a canine model of acute MI, expansion was present in every transmural infarct exceeding a critical weight of 11 % of the total LV weight (7). Attempts to reduce infarct size might prove beneficial in reducing ultimate infarct expansion. There is experimental evidence that captopril reduces myocardial infarct size, an

effect which might be mediated by increased collateral flow to the ischemic zone as well as reduced afterload (96). These observations were not confirmed in a different study using conscious dog model (97). To be effective in reducing infarct size, captopril should b introduced early enough within 6 hours of coronary occlusion.

The effect of captopril on infarct expansion and remodeling was studied in the rat myocardial infarction model (23). It was administered for 3 months following coronary artery ligation. In control group, LV end-diastolic pressure rose progressively paralleling infarct size. In captopril-treated rats, LV end-diastolic pressure remained within normal limits (apart from animals with extensive infarcts > 45 % of the LV surface). Mean arterial pressure and total peripheral resistance were reduced and stroke volume and cardiac output maintained in animals treated with captopril. Left ventricular volumes of treated rats were significantly less than those of untreated. Administration of captopril ameliorated the reduction in forward output in all but those rats with extensive infarcts, LV chamber stiffness, inversely proportional to infarct size, was normalized by chronic captopril therapy. Thus, captopril therapy reduced dilation and improved performance in rats with chronic myocardial infarction. Both captopril (100) and enalapril (101) improved survival in the rat model of myocardial infarction. Captopril given between 3 weeks and 3 months after coronary artery ligation in rats reduced LV mass, LV end-diastolic pressure, mean arterial pressure and total peripheral resistance and maintained cardiac output and heart rate (102). It also reduced LV end-diastolic volume of ventricles with moderate infarcts increasing the ejection fraction index. Beneficial hemodynamic effects of captopril after experimental MI were superior to effects of

hydralazine (103).

In this study it was chosen to start captopril 2 days after creation of experimental myocardial infarction in dogs. Commencement of treatment between 2 and 3 weeks in other studies, particularly in a rat model of infarction, where infarct expansion is well under way at the time, might be expected to have less effect on reducing infarct expansion. By attenuating early infarct expansion during earlier administration, captopril might be expected to have additional beneficial effect on the ultimate outcome. Topographic indices in this study were significantly improved with captopril in comparison to control group. Expansion index was significantly decreased with captopril over the 6 week period, compared to control group where it increased. Captopril also prevented scar thinning which was marked in the control group. Pathologic specimens from control and captopril treated groups are shown in **Figure 13** and underscore the dramatic effect on LV remodeling.

Captopril also improved the functional status of the LV on quantitative serial 2-D echocardiography. Total LV asynergy as an index of regional contractile function was studied serially at weekly intervals over the 6 week period. Although it decreased marginally by 11 % in the control group between 2 days and 6 weeks, it decreased significantly by 48 % ($p<0.001$) in captopril treated group. Global LV ejection fraction, an index of global contractile function or performance, showed significantly greater improvement with captopril than in control group (+34 % versus +16 %, $p<0.05$). Quantitative serial 2-D echocardiograms also showed a marked decrease in expansion and thinning between 2 days and 6 weeks with captopril compared to the placebo controls.

6.3. Hemodynamic effects of captopril in experimental myocardial infarction.

The renin-angiotensin-aldosterone system is known to be activated in congestive heart failure, with elevation of circulating angiotensin II (120). Cardiac function can be affected by alterations in the resistance and capacitance of the peripheral vascular bed. This rationale led to use of an ACE inhibitor, an orally active drug that blocks the enzymatic conversion of angiotensin I to angiotensin II in the treatment of congestive heart failure (121, 122). Both captopril (121, 122) and enalapril (123) have proven to be effective pharmacotherapy for heart failure.

Captopril is a balanced vasodilator, affecting both the arteriolar and venous beds (121), and produces marked reductions in systemic vascular resistance and in the left and right ventricular filling pressures. Cardiac output rises with no change in heart rate (124).

Captopril has been suggested to be a potent vasodilator which can decrease preload and afterload, and improve cardiac function in acute LV failure complicating acute MI (83). Single doses of oral captopril (25 mg) in the above clinical situation produced significant fall in pulmonary capillary wedge pressure and systemic vascular resistance, and increased in cardiac output (83). The intravenous ACE inhibitor teprotide followed by oral captopril significantly decreased peripheral vascular resistance and mean aortic pressure, and increased cardiac output in experimental coronary artery occlusion in dogs (91).

In the present study, captopril was found to have sustained hemodynamic effects after coronary artery occlusion in dogs. Thus, captopril produced marked decrease in mean left atrial pressure, a measure of LV filling pressure or preload, between 2 days and 6 weeks,

significantly greater than that in the control group. In addition, captopril produced a sustained decrease in mean arterial pressure, an index of afterload. In contrast, mean arterial pressure did not change significantly in the control group. Captopril did not have any effect on heart rate. Captopril also resulted in increased plasma renin and decreased aldosterone, to levels different from those in the control group at 6 weeks.

6.4. Infarct collagen

Healing of the canine infarct is associated with twofold increase in infarct hydroxyproline by seven days with a further fivefold increase by 6 weeks (111), at which time a plateau is reached. There is a gradient in hydroxyproline across the infarct with more in infarct centre than margin and border regions (111). There is also a transmural gradient in infarct hydroxyproline at 6 weeks with more in the epicardial than endocardial third, findings in agreement with the histologic findings of healing with fibroblast proliferation and collagen deposition proceeding from the epicardial and lateral borders of the infarct (111).

Different pharmacologic interventions can affect collagen deposition (measured by hydroxyproline content) in the infarct zone. Early therapy after acute MI with anti-inflammatory agents has been shown experimentally to result in scar thinning (28-30). Indomethacin (31) and ibuprofen (28) administered at 15 minutes and 3 hours after coronary artery ligation in dogs, caused marked infarct thinning at six weeks, although indomethacin increases (32) and ibuprofen decreases (33) infarct size in dogs. Early indomethacin therapy in dogs also produced infarct thinning and expansion at 7 days (30).

In a study of the delayed effects of early infarct limiting

therapies on healing after acute MI in dogs (34), NTG, prostacyclin or ibuprofen reduced infarct size and did not reduce infarct collagen content by one week. NTG and prostacyclin reduced infarct expansion while ibuprofen produced more infarct thinning. NTG appeared to increase infarct collagen content at 7 days. Therapy with steroids (29) (high dose of methylprednisolone) in a dog caused marked scar thinning associated with reduction in regional function, without a change in collagen content. The most likely explanations of the effect of anti-inflammatory agents (both non-steroidal and steroids) on infarct expansion include a retardation of the inflammatory response and more rapid resolution of interstitial edema, and possibly some other cellular and biochemical effects.

The results of this study indicate that captopril does not influence collagen deposition during healing post infarction. There was a significant increase in hydroxyproline content in the centre of the infarct zone as compared to normal zone and the same degree of increase in hydroxyproline content in both control and captopril treated dogs. It therefore appears that captopril does not affect the amount of collagen deposited during healing of canine myocardial infarction.

6.5 Conclusion

The clinical importance of ventricular remodeling after acute MI has recently been reviewed (125). Data from other investigators (125) and those presented in this thesis indicate that ACE inhibition is powerful pharmacotherapy to prevent progressive remodeling and interrupt the vicious cycle to more dilatation, congestive heart failure and aneurysm formation in survivors of acute MI. Several clinical studies have indicated that patients with transmural anterior acute MI of moderate size are at greatest risk of marked expansion and remodeling,

(2,82,118,119,125). These patients might benefit from preventive therapy with an ACE inhibitor as captopril.

The findings in this thesis indicate that longterm therapy with ACE inhibitors during healing after AMI have the potential for preventing significant further expansion after the infarction process is over. Furthermore, such therapy also has the potential for preventing late thinning. More important, the findings provide the rationale for early and prolonged application of therapy in relatively small transmural infarcts as are encountered after thrombolytic therapy.

In summary, captopril therapy over 6 weeks after experimental myocardial infarction in a canine model was found to prevent late infarct thinning, decrease infarct expansion and improve LV function. Captopril produced sustained decreases in preload and afterload so that these hemodynamic effects were most likely responsible for the beneficial effects of captopril on LV topography and function. In addition, captopril did not have a deleterious effect on the quantity of collagen deposited in the infarct zone.

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TABLE 1. Determinants of infarct expansion.*

Determinant	Pathophysiologic mechanism	Influencing factors
A. Physical characteristics of the infarct	i Infarct size: large > small ii Transmurality: transmural > subendocardial iii Location: anterior > inferior iv Type: first > subsequent infarct v Age: early phase of healing > late	Severity of coronary artery disease, collateral blood flow, drugs
B. Efficacy of the healing processes	i Inflammatory response ii Collagen deposition iii Collateral circulation iv Nutrient flow	Drugs eg. 1. anti-inflammatory steroidal and non-steroidal agents 2. drugs that damage or strenghten collagen matrix 3. drugs that stimulate or inhibit collagen deposition
C. Strength, duration and frequency of mechanical deformation forces acting on the infarct zone (distension) and stretch vs external restraint	i Greater afterload, preload and contractility of noninfarcted myocardium increase distending infarct zone. ii The higher the heart rate, the greater the frequency of application of mechanical deformation forces. iii The pericardium, adjacent extracardiac structures, and pericardial fluid provide external restraint.	Hypertension, drugs, exercise, heart rate (Treppe effect)

* Modified from reference 20.

TABLE 2. Theurapeutic interventions which can protentially reduce infarct expansion.*

Theurapeutic goal	Agents
Decreased infarct size	NTG
Increased collateral flow	NTG
Decreased preload	NTG, ACE-I
Decreased afterload	NTG, ACE-I
Decreased chamber size	NTG, ACE-I
Decreased heart rate	Beta blockers, CCB
Decreased contractility	Beta blockers, CCB

NTG = nitroglycerin
ACE-I = angiotensin-converting enzyme inhibitors
CCB = calcium channel blockers

* Modified from reference 20.

TABLE 3. Characteristics of the control group.

Exp. No.	Age (yr)	Sex (M/F)	Weight (kg)	Artery occluded	Exp. duration (days)
1	4	M	21.6	LAD	44
2	2	F	19.5	LAD	44
3	3	M	22.0	LAD	44
4	4	F	15.5	LAD	23 (stroke)*
5	1	M	19.5	LAD	51
6	1	M	15.5	LAD	44
7	4	F	21.5	LAD	23 (accidental injury)*
8	1	F	18.3	LAD	44
9	0.7	F	17.5	LAD	44
10	3	F	19.5	LAD	44
11	0.6	M	25.0	LAD	37
12	4	F	21.5	LAD	44
13**	4	F	19.3	LAD	9
14**	1	M	21.0	LAD	11
15**	0.6	F	20.5	LAD	16

* Sacrificed before scheduled date for humane reasons (excluded from analysis).
** Premature deaths (excluded from analysis).

Exp., experiment; LAD, left anterior descending coronary artery.

TABLE 4. Characteristics of the captopril treated group.

Exp. No.	Age (yr)	Sex (M/F)	Weight (kg)	Artery occluded	Exp. duration (days)
16	3	M	18.0	LAD	43
17	2	F	22.5	LAD	43
18	4	F	23.0	LAD	48
19	0.7	M	21.5	LAD	43
20*	0.7	M	20.5	LAD	25
21	2	M	22.5	LAD	43
22	2	F	20.7	LAD	43
23	0.4	M	20.3	LAD	48
24	2	M	22.5	LAD	44
25*	1	M	18.5	LAD	32
26	0.4	M	19.0	LAD	46
27	3	M	17.5	LAD	41
28†	4	F	20.0	LAD	43
29*	3	F	21.5	LAD	12
30*	1	F	24.0	LAD	12

* Early premature cage deaths, most likely due to dysrhythmias (excluded from analysis).
† No infarction (excluded from analysis).

Exp., experiment; LAD, left anterior descending coronary artery.

Table 5. Hemodynamic parameters in the control and captopril groups: Heart rate (beats/min).

Control group (n=10)									Captopril Group (n=10)								
Experiment No.	1	2	3	4	5	6	7	8	Experiment No.	1	2	3	4	5	6	7	8
1	120	100	72	93	105	84	72	78	16	108	138	96	84	93	96	90	72
2	96	108	126	93	87	108	72	102	17	102	108	96	96	90	90	90	96
3	90	168	96	93	84	93	68	78	18	120	126	90	69	90	90	112	99
5	90	126	93	84	114	84	84	84	19	126	144	69	90	96	78	81	90
6	138	120	75	93	66	72	93	75	21	120	132	66	66	84	66	78	78
8	126	138	108	69	90	69	108	120	22	144	168	105	84	78	60	93	96
9	102	150	72	69	114	102	90	72	23	126	132	96	72	96	84	72	80
10	156	174	75	87	91	114	96	96	24	60	150	93	84	75	90	90	96
11	150	168	114	114	75	114	84	84	26	108	138	78	102	78	63	108	108
12	102	150	108	87	84	96	92	96	27	96	144	120	126	114	102	78	90
Mean	117	140	94	88	91	94	86	89	Mean	120	139	91	87	89	82	89	91
± SD	±25	±26	±20	±13	±16	±16	±13	±15	± SD	±17	±16	±16	±18	±12	±12	±13	±11

1 = pre-operative; 2 = post-operative; 3 = 5-9 days; 4 = 12-16 days; 5 = 19-23 days; 6 = 26-30 days; 7 = 33-37 days; 8 = 40-44 days.

Table 6. Hemodynamic parameters in the control and captopril groups: Mean arterial pressure (mm Hg).

Control group (n=10)									Captopril Group (n=10)								
Experiment No.	1	2	3	4	5	6	7	8	Experiment No.	1	2	3	4	5	6	7	8
1	116	128	115	116	110	112	108	108	16	125	125	115	92	97	99	96	92
2	108	105	123	120	118	115	109	112	17	111	112	100	102	128	98	92	87
3	111	117	130	145	130	130	125	120	18	115	124	98	100	98	102	100	106
5	117	110	155	108	112	110	106	108	19	123	133	112	110	108	98	96	104
6	115	112	143	115	110	108	110	105	21	106	130	112	110	108	106	100	96
8	114	127	101	100	102	123	104	109	22	111	114	132	112	112	114	116	113
9	106	107	99	135	120	118	122	132	23	103	111	88	96	95	106	102	105
10	103	143	99	93	102	105	108	113	24	117	124	119	112	110	116	110	116
11	109	113	88	108	108	110	122	112	26	112	119	103	94	84	90	94	117
12	101	101	100	100	98	102	110	126	27	103	106	78	82	80	76	84	104
Mean	110	116	115	114	111	113	112	115	Mean	113	120	106	101	102	101	99	104
± SD	6	13	22	16	10	9	8	9	± SD	8	9	16	10	14	11	9	10

1 = pre-operative; 2 = post-operative; 3 = 5-9 days; 4 = 12-16 days; 5 = 19-23 days; 6 = 26-30 days; 7 = 33-37 days; 8 = 40-44 days.

Table 7. Hemodynamic parameters in the control and captopril groups: Summary of initial and final systolic and diastolic pressures (mm Hg).

Control group (n=10)				Captopril Group (n=10)			
Experiment No.		Pre-operative	Post-operative	Final	Experiment No.	Pre-operative	Post-operative	Final
1		140/96	160/112	146/89	16	150/112	150/112	124/76
2		124/96	120/98	152/92	17	140/96	128/100	120/80
3		144/94	150/100	144/108	18	145/100	140/108	146/80
5		150/100	150/90	132/92	19	170/100	176/112	140/84
6		145/100	152/90	136/90	21	145/86	156/114	134/77
8		146/98	164/108	148/90	22	148/92	140/100	140/100
9		139/90	128/96	180/108	23	130/90	128/102	140/88
10		140/85	172/128	152/94	24	150/100	160/104	164/96
11		148/90	132/104	152/92	26	145/96	148/104	[illegible]/96
12		136/84	126/88	170/104	27	130/90	140/90	[illegible]/90
Mean ± SD	S	141±7	145±18	151±14	Mean ± SD	145±11	147±15	[illegible]±14
	D	93±6	101±12	96±8		96±7	105±7	87±9

D, diastolic; S, systolic.

Table 8. Hemodynamic parameters in the control and captopril groups: Mean left atrial pressure (mm Hg).

	Control group (n=10)									Captopril Group (n=10)							
Exp. No.	1	2	3	4	5	6	7	8	Exp. No.	1	2	3	4	5	6	7	8
1	5	9	11	13	11	10	11	10	16	5	11	11	5	4	4	6	6
2	5	10	10	11	11	10	10	9	17	6	11	6	4	4	4	6	6
3	6	15	11	10	8	7	7	8	18	5	11	6	5	5	8	5	5
5	6	11	12	8	9	9	8	6	19	6	10	6	6	6	4	3	5
6	5	16	11	10	10	10	10	10	21	7	11	6	6	6	7	7	6
8	5	11	11	6	6	6	5	6	22	5	11	6	5	6	8	7	8
9	7	11	9	11	11	10	15	18	23	4	12	7	6	6	8	9	11
10	4	20	17	8	10	9	8	8	24	5	16	6	10	6	6	6	3
11	6	8	9	6	7	6	6	9	26	6	15	4	5	6	6	4	4
12	5	14	24	22	15	16	15	13	27	5	15	7	7	6	7	3	4
Mean	5.4	12.5	12.5	10.5	9.8	9.3	9.5	9.7	Mean	5.4	12.3	6.5	5.9	5.5	6.2	5.6	5.8
± SD	±0.8	±3.7	±4.6	±4.6	±2.5	±2.9	±3.4	±3.6	± SD	±0.8	±2.2	±1.8	±1.7	±0.9	±1.7	±1.9	±2.3

Exp., experiment; 1 = pre-operative; 2 = post-operative; 3 = 5-9 days; 4 = 12-16 days; 5 = 19-23 days; 6 = 26-30 days; 7 = 33-37 days; 8 = 40-44 days.

TABLE 9. Infarct or scar size data in the control group.

Exp. No.	LV Mass (g)	Occluded Bed Mass (g)	Infarct Mass (g)	Occluded Bed/LV (%)	Infarct/ LV (%)	Infarct/ Occluded Bed (%)
1	74.04	16.61	5.78	22.43	7.80	34.78
2	62.28	17.02	5.77	27.33	9.27	33.91
3	79.55	10.77	4.56	13.54	5.73	42.33
5	54.33	10.23	3.58	18.83	6.59	34.97
6	45.22	6.47	3.02	14.30	6.68	46.69
8	61.87	8.43	0.70	13.63	1.13	8.27
9	64.17	7.97	3.94	12.42	6.14	49.42
10	55.71	5.34	3.16	9.58	5.67	59.16
11	89.92	14.69	4.24	16.34	4.71	28.83
12	67.19	7.98	5.07	11.87	7.55	63.56
Mean	65.43	10.55	3.98	16.03	6.13	40.19
± SD	±13.02	±4.18	±1.51	±5.41	±2.17	±15.92

Exp., experiment; LV, left ventricular.

TABLE 10. Infarct or scar size data in the captopril treated group.

Exp. No.	LV Mass (g)	Occluded Bed Mass (g)	Infarct Mass (g)	Occluded Bed/LV (%)	Infarct/ LV (%)	Infarct/ Occluded Bed (%)
16	70.84	23.60	0.50	33.31	0.71	2.12
17	82.03	14.89	9.95	18.16	12.12	66.78
18	87.29	16.66	3.73	19.09	4.27	22.37
19	85.20	18.90	2.56	22.18	3.01	13.55
21	77.53	23.25	6.08	29.99	7.84	26.15
22	68.65	12.62	8.73	18.38	12.72	69.19
23	76.10	19.73	7.11	25.93	9.35	36.05
24	92.64	9.69	4.15	10.46	4.48	42.85
26	71.04	9.19	0.22	12.94	0.31	2.36
27	61.96	5.27	2.09	8.51	3.37	39.64
Mean	77.33	15.38	4.51	19.90	5.82	32.11
± SD	±9.50	±6.18	±3.36	±8.14	±4.45	±23.63

Exp., experiment; LV, left ventricular.

TABLE 11. Topographic measurements in the control group: Parameters 1 to 8.

Exp. No.	1 Area of Infarct (cm^2)	2 Circum of Infarct (cm)	3 Endo Infarct Segment (cm)	4 Normal Endo Segment (cm)	5 Infarct Area/LV Area (%)	6 Infarct Thickness (cm)	7 Normal Wall Thickness (cm)	8 Infarct/ Normal Wall Thickness Ratio
1	1.64	5.12	3.09	4.61	10.00	1.10	1.40	0.79
2	1.74	5.97	3.78	4.13	16.90	0.60	1.30	0.46
3	2.55	6.44	3.30	2.99	22.20	0.65	1.40	0.46
5	3.60	7.01	2.00	5.51	25.50	1.00	1.40	0.71
6	1.44	4.22	2.85	4.06	17.70	0.50	0.80	0.63
8	0.73	3.02	1.33	7.47	5.30	0.65	1.15	0.57
9	1.18	5.66	1.18	3.88	17.70	0.50	0.80	0.63
10	1.30	4.44	1.72	5.89	10.40	0.30	0.70	0.43
11	1.76	4.80	2.08	4.77	10.90	0.55	1.05	0.52
12	2.64	7.67	4.53	2.92	25.20	0.60	1.25	0.48
Mean	1.86	5.44	2.59	4.62	16.18	0.65	1.13	0.57
± SD	±0.84	±1.40	±1.10	±1.38	±6.89	±0.24	±0.27	±0.12

Circum, circumference; Endo, endocardial; Exp., experiment; LV, left ventricular.

TABLE 12. Topographic measurements in the control group: Parameters 9 to 16.

Exp. No.	9 Area of Inner LV Ring (cm^2)	10 Circum of Inner LV Ring (cm)	11 Area of Outer LV Ring (cm^2)	12 Circum of Outer LV Ring (cm)	13 Area of LV Tissue (cm^2)	14 Max Trans-mural Extent of Infarct (%)	15 Area of Normal Tissue (cm^2)	16 Expansion Index Ratio
1	3.48	7.70	15.90	14.40	16.40	100	14.76	2.92
2	3.87	7.91	14.14	13.42	10.27	85	8.53	3.09
3	2.68	6.29	14.18	13.54	11.50	85	8.95	2.84
5	3.52	7.51	17.63	15.15	14.11	100	10.51	2.47
6	3.13	6.91	11.24	12.47	8.12	100	6.68	2.43
8	2.29	8.80	16.06	14.28	13.78	100	13.05	3.04
9	0.42	5.06	7.08	9.90	6.66	100	5.48	2.82
10	2.54	7.61	15.07	10.86	12.53	100	11.23	2.16
11	2.62	6.85	18.84	12.62	16.22	100	14.46	2.52
12	1.93	7.45	12.41	12.84	10.48	100	7.84	2.91
Mean	2.65	7.21	14.26	12.95	12.01	97	10.15	2.72
± SD	±0.99	±1.01	±3.38	±1.61	±3.24	±6.32	±3.21	±0.31

Exp., experiment; LV, left ventricular.

TABLE 13. Topographic measurements in the captopril treated group: Parameters 1 to 8.

	1	2	3	4	5	6	7	8
Exp. No.	Area of Infarct (cm^2)	Circum of Infarct (cm)	Endo Infarct Segment (cm)	Normal Endo Segment (cm)	Infarct Area/LV Area (%)	Infarct Thickness (cm)	Normal Wall Thickness (cm)	Infarct/Normal Wall Thickness Ratio
16	0.38	1.68	0.55	4.09	3.35	1.25	1.30	0.96
17	4.53	9.13	4.28	3.37	33.78	0.85	1.05	0.81
18	2.25	6.07	1.97	3.82	17.32	1.30	1.30	1.00
19	1.85	4.66	1.93	4.05	10.72	1.15	1.25	0.92
21	1.68	4.67	2.21	9.16	10.47	0.60	1.10	0.55
22	3.46	8.33	5.79	5.12	29.62	0.55	0.95	0.58
23	2.48	5.69	1.73	4.95	23.66	0.85	0.90	0.94
24	1.25	5.33	0.37	7.70	8.05	0.55	0.70	0.79
26	0.47	2.69	0.00	7.02	3.21	0.90	1.10	0.82
27	1.33	3.60	1.03	4.89	11.08	1.00	1.15	0.87
Mean	1.97	5.19	1.99	5.42	15.13	0.90	1.08	0.82
± SD	±1.29	±2.31	±1.81	±1.91	±10.67	±0.28	±0.19	±0.15

Circum, circumference; endo, endocardial; LV, left ventricular.

TABLE 14. Topographic measurements in the captopril treated group: Parameters 9 to 16.

Exp. No.	9 Area of Inner LV Ring (cm^2)	10 Circum of Inner LV Ring (cm)	11 Area of Outer LV Ring (cm^2)	12 Circum of Outer LV Ring (cm)	13 Area of LV Tissue (cm^2)	14 Max Transmural Extent of Infarct (%)	15 Area of Normal Tissue (cm^2)	16 Expansion Index Ratio
16	1.27	4.64	12.60	12.78	11.33	46	10.95	2.16
17	4.13	7.65	15.81	14.39	11.68	100	7.15	2.34
18	1.04	5.79	14.04	13.33	12.99	96	10.74	1.61
19	0.72	5.98	17.96	15.07	17.25	78	15.40	1.74
21	8.47	11.37	24.53	17.74	16.05	100	14.37	2.10
22	8.90	10.91	20.57	16.45	11.68	100	8.22	2.69
23	2.64	6.68	13.11	13.03	10.48	100	8.00	2.43
24	3.45	8.07	18.97	15.68	15.52	100	14.27	2.46
26	1.73	7.02	16.37	14.45	14.64	41	14.17	1.86
27	1.18	5.92	13.18	13.14	12.00	100	10.67	1.96
Mean	3.35	7.40	16.71	14.61	13.36	86.1	11.39	2.14
± SD	±3.02	±2.20	±3.85	±1.64	±2.33	±23.49	±3.01	±0.35

Circum, circumference; Exp., experiment; LV, left ventricular.

TABLE 15. Topographic data from 2-D echocardiograms in the control group.

Exp. No.	Expansion index						Thinning ratio					
	1	2	3	4	5	6	1	2	3	4	5	6
1	2.61	2.62	2.60	2.69	2.84	2.90	0.80	0.51	0.52	0.48	0.54	0.56
2	2.26	2.20	2.20	2.25	2.30	2.40	0.75	0.72	0.67	0.67	0.59	0.52
3	2.20	2.27	2.29	2.27	2.40	2.50	0.86	0.72	0.68	0.70	0.70	0.70
5	2.19	2.93	2.33	3.18	3.51	3.77	0.71	0.65	0.68	0.67	0.60	0.58
6	2.07	2.24	2.22	2.23	2.64	2.95	0.68	0.70	0.50	0.54	0.51	0.52
8	2.79	2.92	2.96	2.93	2.92	3.04	0.83	0.87	0.75	0.65	0.68	0.58
9	2.35	3.31	3.69	2.93	3.21	3.18	0.99	0.89	0.89	0.75	0.66	0.65
10	2.40	2.60	2.60	2.70	2.82	2.96	0.90	0.91	0.81	0.70	0.74	0.67
11	2.07	2.24	2.22	2.33	2.43	2.52	0.98	0.91	0.80	0.87	0.82	0.84
12	1.98	2.79	2.85	2.80	2.91	2.91	0.85	0.85	0.81	0.75	0.71	0.70
Mean	2.29	2.61	2.60	2.63	2.80	2.91	0.84	0.77	0.71	0.68	0.66	0.63
± SD	±0.25	±0.38	±0.47	±0.34	±0.38	±0.40	±0.10	±0.13	±0.13	±0.11	±0.10	±0.10

Exp., experiment.

Time intervals, 1 = 2 days, 2 = 2 weeks, 3 = 3 weeks, 4 = 4 weeks, 5 = 5 weeks, 6 = 6 weeks.

TABLE 16. Topographic data from 2-D echocardiograms in the captopril group.

Exp. No.	Expansion index						Thinning ratio					
	1	2	3	4	5	6	1	2	3	4	5	6
16	2.52	2.19	2.15	2.11	2.12	2.16	0.74	0.83	0.81	0.81	0.84	0.81
17	2.50	2.65	2.96	2.42	2.30	1.87	0.91	0.89	0.80	0.72	0.73	0.69
18	2.34	2.34	2.20	2.18	1.70	1.61	0.88	0.79	0.80	0.73	0.79	0.85
19	2.52	2.73	2.70	2.67	2.07	1.74	0.62	0.80	0.81	0.83	0.71	0.75
21	2.29	1.89	1.90	1.82	1.88	1.85	0.86	0.78	0.76	0.85	0.73	0.84
22	2.56	2.72	2.29	1.61	1.75	1.69	0.72	0.84	0.79	0.75	0.81	0.78
23	2.01	1.57	1.75	1.77	1.78	1.73	0.82	0.70	0.81	0.73	0.87	0.78
24	2.20	1.86	1.96	1.64	1.74	1.86	0.85	0.88	0.92	0.87	0.79	0.79
26	2.29	2.07	2.10	1.92	1.89	1.86	0.95	0.80	0.79	0.89	0.78	0.86
27	1.83	1.92	2.23	1.96	2.15	1.87	0.98	0.83	0.84	0.87	0.91	0.84
Mean	2.31	2.19	2.22	2.01	1.94	1.82	0.83	0.81	0.81	0.81	0.80	0.80
± SD	±0.24	±0.41	±0.36	±0.34	±0.21	±0.15	±0.11	±0.05	± 0.04	±0.07	±0.06	±0.05

Exp., experiment.

Time intervals, 1 = 2 days, 2 = 2 weeks, 3 = 3 weeks, 4 = 4 weeks, 5 = 5 weeks, 6 = 6 weeks.

TABLE 17. Functional data from 2-D echocardiograms in the control group.

Exp. No.	Total LV asynergy (%)						LV Ejection Fraction (%)					
	1	2	3	4	5	6	1	2	3	4	5	6
1	6.2	4.4	3.7	3.7	4.9	4.8	32.0	43.5	46.2	47.1	44.5	48.6
2	12.2	12.5	11.9	11.2	11.2	6.7	45.8	44.2	40.0	46.5	50.5	51.1
3	12.7	11.4	10.4	10.9	10.6	10.7	44.1	50.9	51.9	49.6	43.1	52.2
5	11.3	10.7	9.3	9.5	10.3	10.3	38.3	45.5	44.5	47.1	45.0	44.5
6	9.2	7.1	6.0	3.6	4.9	5.3	38.0	41.8	45.7	44.8	51.0	42.8
8	10.5	16.2	18.5	15.7	14.6	14.5	47.5	42.6	48.9	49.2	38.4	45.5
9	15.1	17.4	17.3	16.1	14.9	14.9	32.9	38.2	39.8	49.9	47.3	46.3
10	16.8	17.3	17.9	14.4	14.2	14.4	36.4	42.7	42.2	46.4	44.7	36.9
11	12.9	13.1	13.8	14.6	14.9	11.2	30.9	39.6	40.0	37.1	42.3	42.6
12	14.3	14.8	14.8	14.7	14.8	15.2	38.9	37.5	38.6	39.4	29.9	35.3
Mean	12.1	12.4	12.4	11.4	11.5	10.8	38.5	42.7	43.8	45.7	43.7	44.6
SD	±3.0	±4.3	±5.1	±4.7	±3.9	±4.0	±5.8	±3.9	±4.4	±4.3	±6.1	±5.5

Exp., experiment, LV, left ventricular.

Time intervals, 1 = 2 days, 2 = 2 weeks, 3 = 3 weeks, 4 = 4 weeks, 5 = 5 weeks, 6 = 6 weeks.

TABLE 18. Functional LV data from 2-D echocardiograms in the captopril group.

Experiment No.	Total LV asynergy (%)						LV ejection fraction (%)					
	1	2	3	4	5	6	1	2	3	4	5	6
16	8.7	7.4	4.7	3.4	1.4	1.5	48.2	57.1	52.7	50.8	64.7	60.2
17	8.8	4.2	4.8	3.3	2.8	2.2	51.2	58.9	59.2	60.3	60.0	59.5
18	4.7	6.1	4.6	2.6	3.4	2.3	40.3	52.2	55.6	65.4	60.1	63.8
19	9.6	9.3	5.0	6.1	5.3	4.5	42.4	50.3	50.3	63.7	58.0	63.9
21	12.5	11.6	7.1	6.7	6.2	3.9	46.2	51.1	62.5	61.5	60.6	64.6
22	20.8	18.5	17.2	14.1	14.7	10.9	32.4	25.1	25.8	35.5	32.9	33.9
23	12.1	10.2	10.9	7.6	8.3	9.4	35.5	33.6	37.2	35.6	33.9	43.0
24	11.5	12.2	8.1	8.2	6.1	4.9	37.5	42.0	52.0	51.0	49.0	52.7
26	14.0	13.9	13.2	13.8	12.7	13.0	36.1	42.7	41.8	41.3	42.5	46.0
27	19.6	18.9	17.7	16.1	11.0	11.8	32.4	44.5	53.9	51.0	56.5	50.5
Mean	12.2	11.2	9.3	8.2	7.2	6.4	40.2	45.8	49.1	51.6	51.8	50.8
± SD	±4.9	±4.9	±5.2	±4.9	±4.4	±4.4	±6.6	±10.5	±11.1	±11.2	±11.2	±10.4

LV, left ventricular.

Time intervals, 1 = 2 days, 2 = 2 weeks, 3 = 3 weeks, 4 = 4 weeks, 5 = 5 weeks, 6 = 6 weeks.

TABLE 19. Data on myocardial hydroxyproline (OHP) content in the two groups.

Control (n=10)					Captopril (n=10)				
Experiment No.	OHP mg/g dry weight C	M	B	N	Experiment No.	OHP mg/g dry weight C	M	B	N
1	38.50	20.69	9.65	5.34	16	27.38	12.31	8.46	6.67
2	42.04	28.33	6.24	5.63	17	31.96	8.57	11.26	5.97
3	26.96	11.12	9.79	4.96	18	33.41	13.30	6.97	7.29
5	44.09	35.39	11.62	8.83	19	49.11	27.98	11.98	4.20
6	47.56	29.02	12.68	4.36	21	38.79	30.87	19.15	5.76
8	27.46	24.63	23.50	7.27	22	37.24	13.45	29.20	4.55
9	37.01	35.12	15.07	5.34	23	16.12	19.84	15.83	4.09
10	45.38	41.41	29.05	3.91	24	60.01	58.51	29.40	6.37
11	31.64	17.79	5.49	3.88	26	20.83	15.94	10.96	5.65
12	33.73	38.96	11.83	5.35	27	41.26	33.85	10.16	4.83
Mean	37.44	28.25	13.49	5.49	Mean	35.61	23.46	15.34	5.54
± SD	±7.37	±9.77	±7.43	±1.53	± SD	±12.94	±15.02	±8.14	±1.09

C = center, M = margin, B = border, N = normal.

Table 20. Summary of plasma renin profile.

Timing	Plasma renin activity (ng/ml/hour)	
	Control (n=5)	Captopril (n=5)
Pre-operative	1.4 ± 0.9	1.6 ± 0.7
Post-operative (Post-ligation)	3.5 ± 1.1	4.1 ± 1.2
6 Weeks	2.9 ± 1.3	7.5 ± 2.9

Table 21. Summary of plasma aldosterone profile.

Timing	Arterial plasma aldosterone activity (pmol/L)*	
	Control (n=5)	Captopril (n=5)
Pre-operative	197 ± 141	142 ± 82
Post-operative (Post-ligation)	450 ± 292	510 ± 216
6 weeks	149 ± 100	14 ± 26

* 1 pmol/L = about 360 pg/L