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Effect of Prolonged Inotropic Stimulation on Ventricular Remodeling During Healing After Myocardial Infarction in the Dog: Mechanistic Insights

BODH I. JUGDUTT, MD, MSc, FACC, MOHAMMAD I. KHAN, MBBS,
S. JOANNE JUGDUTT, BA, GORDON E. BLINSTON, PHD

Edmonton, Alberta, Canada

Objectives. **We hypothesized that positive inotropic stimulation during healing after myocardial infarction might increase contractile pull on the infarct segment, increase expansion and promote ventricular dilation.**

Background. **The effect of prolonged inotropic stimulation on left ventricular remodeling during healing after myocardial infarction has not been studied.**

Methods. **The effects of 6 weeks of inotropic stimulation on in vivo changes in left ventricular topography, function and mass (serial two-dimensional echocardiograms), hemodynamic variables, postmortem topography (planimetry) and collagen (hydroxyproline content) were studied in 36 chronically instrumented dogs randomized, 2 days after small anterior infarction, to digoxin (0.125 mg daily) and no digoxin (control group).**

Results. **Heart rate and arterial and left atrial pressures were similar in the two groups, but the first derivative of left ventricular pressure (peak dP/dt), systolic thickening of the noninfarct wall and systolic thinning of the infarct wall were higher in the digoxin group during the 6 weeks. At 6 weeks, infarct scar size and collagen content were similar in both groups, but the digoxin group had more infarct expansion and thinning. Between 2 days and 6 weeks, the digoxin group showed more in vivo diastolic infarct expansion, thinning and bulging; more aneurysm but less global dilation and increase in mass; and no change in ejection fraction. The effects of inotropic stimulation on remodeling were more marked in infarcts with 100% than 85% transmurality.**

Conclusions. **Prolonged inotropic stimulation with digoxin during healing after small anterior infarction increases infarct bulging without decreasing infarct collagen content and preserves global ventricular size, mass and systolic function.**

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Expansion of the infarct area leads to aneurysm formation and left ventricular dilation after myocardial infarction (1–3). Bulging of the infarct zone, which initially occurs only in systole, subsequently develops in diastole and causes diastolic shape distortion (4). Prolonged positive inotropic stimulation, which increases the contractility of the noninfarct area, might exert "traction" or "pull" on the infarct zone during systole and result in more infarct stretching and thinning and more systolic and diastolic bulging. To date, there has been no systematic study of the effects of prolonged inotropic stimulation on remodeling during healing after infarction.

Therefore, our main purpose was to determine whether prolonged inotropic stimulation during healing after anterior infarction increases in vivo diastolic stretching and thinning of the infarct segment and results in more infarct bulging in a well defined dog model (5–7). In addition, we studied the effects on 1) in vivo global remodeling, systolic function and ventricular mass; and 2) postmortem topography and infarct collagen content. We used digoxin as the inotropic agent (8).

Methods

Experimental preparation. Experiments were approved by the institutional animal welfare committee and conformed to the "Position of the American Heart Association on Research Animal Use" adopted by the Association in November 1984. Forty-five healthy mongrel dogs (16 to 29 kg) of either gender were anesthetized (sodium pentobarbital, 30 mg/kg body weight intravenously) and instrumented through a left lateral thoracotomy, as described previously (5–7). Polyethylene catheters were placed in the external jugular vein, internal carotid artery and left atrium. The mid-left anterior descending coronary artery was ligated. Metal beads were sutured onto the epicardial surfaces in the short-axis plane at the midventricular level for consistent echocardiographic imaging. More transmural infarction was produced in 12 dogs by ligating visible epicardial collateral vessels (6). The pericardium and chest

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Address for correspondence: Dr. Bodh I. Jugdutt, 2C2.43 Walter MacKenzie Health Sciences Centre, Division of Cardiology, University of Alberta, Edmonton, Alberta, Canada T6G 2R7.

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were closed, and all dogs were given penicillin (1 million U) and streptomycin (1 g) intramuscularly.

Protocol. Two days after infarction, the 40 survivors were randomized to receive digoxin (0.125 mg orally, once daily [digoxin group]) or no digoxin (control group) for 6 weeks. The dose of digoxin was within the effective therapeutic range for dogs in heart failure (9) and was much lower than the dose (0.0125 mg/kg or 0.29 mg in a 23-kg dog) associated with enhanced susceptibility to arrhythmia on programmed ventricular stimulation after anterior infarction (10). At 6 weeks, the 36 survivors were anesthetized. The hearts were arrested in diastole (with an overdose of intravenous potassium chloride), removed, washed in normal saline solution and weighed.

In vivo measurements during healing. As described previously (5–7), serial two-dimensional echocardiograms (Toshiba SSH-65A; 3.5-MHz transducer), electrocardiograms (Gould recorder) and hemodynamic variables (Statham P23Db for left atrial and arterial pressures) were recorded in the conscious dog, standing in a jacket, at baseline (before operation and occlusion), 2 days after infarction (before randomization) and weekly for 6 weeks. Echocardiograms included parasternal long- and short-axis planes (at mitral, chordal, midpapillary, low papillary and apical levels) and apical four- and two-chamber views. The positive peak of the first derivative of left ventricular pressure (peak dP/dt [mm Hg/s]) was recorded before and 1, 3 and 6 weeks after occlusion by advancing a micromanometer-tipped catheter (Millar Instruments) through the left atrial line into the ventricle.

Analysis of echocardiograms. As described previously (6,7), coded echocardiograms were analyzed in double-blind manner. Briefly, tracings of endocardial and epicardial contours of videotaped images were made with a light pen (Diasonics CardioRevue) at end-diastole and end-systole and copied on plastic overlays, together with positions of anatomic landmarks (e.g., papillary muscles). *Asynergy*, defined as *akinesia* (no systolic inward motion and thickening) or *dyskinesia* (systolic outward motion and thinning), or both, was marked on each endocardial diastolic outline. The extent of asynergy on each short-axis outline was digitized (Hewlett-Packard 9878A and 9835A) and used to compute the endocardial surface area of asynergy by a three-dimensional reconstruction algorithm. Outlines of five short-axis and two long-axis images were used to compute volumes by means of a modified Simpson's rule algorithm. *Global ejection fraction* was calculated as end-diastolic volume minus end-systolic volume divided by end-diastolic volume. *Systolic thickening*, defined as wall thickness at end-systole minus thickness at end-diastole divided by thickness at end-diastole (11), was calculated. *Interobserver error* was <5% in marking asynergy, segment length, wall thickness and area of outlines, in agreement with previous studies (6,7). *Topographic measurements* were made on end-diastolic contours of short-axis images at the papillary level. Expansion index (ratio of the lengths of the asynergy-containing and non–asynergy-containing segments demarcated by papillary muscle landmarks), thinning ratio (ratio of the average thicknesses of the asynergic and nonasynergic zones) and the depth of regional bulging in the asynergic zone were computed (4,6,7). *Left ventricular aneurysm* was defined as the presence of diastolic bulge with further bulging and thinning in systole. *Left ventricular mass* was computed as the difference between end-diastolic volumes of epicardial and endocardial shells multiplied by an assumed specific gravity of 1.05 g/ml (7).

Postmortem measurement of scar size, geometry and collagen content. As described previously (5–7), risk region was measured on postmortem coronary arteriograms recorded on radiographs of the whole heart and transverse sections (1 to 1.5 cm thick). Outlines of ventricular rings, risk regions and infarct scars made on plastic overlays were planimetered (Hewlett-Packard 9835A computer and 9874A digitizer) for deriving infarct size, topographic variables (wall thicknesses, cavity areas, endocardial segment lengths and angular extent of scar) and average short-axis maps (6,7). *Transmurality* was defined as the average of ratios of maximal infarct thickness and full wall thickness for each infarcted ring and expressed as percent (6,7). Contours of the left ventricular epicardium and endocardium made from whole-heart radiographs were digitized to measure the depth of the apical bulge in the long axis and generate average long-axis maps (7). *Histopathologic analysis* for infarction and collagen was done on triplicate 5-μm sections of infarct tissue that were stained with hematoxylin and eosin, Mallory's stain or Masson's trichrome (5–7). *Myocardial hydroxyproline* (mg/g dry weight), a collagen marker, was measured in samples (100 to 200 mg) from the center of the infarct scar and nonoccluded zone (5–7).

Statistics. Data were analyzed in blinded manner by 1) two-way analysis of variance (ANOVA) and two-way repeated measures ANOVA for comparing data within and between groups, with multiple comparisons using the Student-Neuman-Keuls test; and 2) chi-square test for the difference in event frequency between groups. Results are presented as mean ± SEM. Statistical significance was set at $p < 0.05$.

Results

Study groups. Of the 40 dogs that were randomized at 2 days, 4 died within 2 weeks and were excluded. Data from 36 dogs that were killed at 6 weeks were analyzed. There were 18 dogs in each group, and 6 in each group had collateral ligation as well.

Postmortem remodeling and collagen content. At 6 weeks, infarct scar size, transmurality and regional hydroxyproline content were similar (p = NS) in the two groups (Table 1). Left ventricular mass was less in the digoxin group (82.8 vs. 101.4 g, $p < 0.0007$). As expected, dogs with collateral ligation had avascular apical zones on coronary arteriograms (6) and 100% transmural infarcts (Table 1). However, infarct mass (in grams and percent left ventricle) was similar in subgroups with or without collateral ligation (Table 1). Regional topographic maps for digoxin (Table 2) showed longer extent of infarct scar ($p < 0.005$), more endocardial bulge at the apex ($p < 0.001$), larger cavity area ($p < 0.0005$), less infarct wall thickness in the

Table 1. Infarct Scar Size, Transmurality and Hydroxyproline (mean ± SEM)

	Control Group			Digoxin Group		
	No CL (n = 12)	CL (n = 6)	All (n = 18)	No CL (n = 12)	CL (n = 6)	All (n = 18)
Infarct scar mass (g)	5.7 ± 0.7	5.8 ± 0.4	5.7 ± 0.5	4.3 ± 0.8	5.0 ± 1.1	4.9 ± 0.6
Risk region mass (g)	11.4 ± 1.4	7.3 ± 0.5	10.2 ± 1.0	0.9 ± 1.7	7.1 ± 1.2	9.6 ± 1.3
LV mass (g)	100.7 ± 4.8	102.8 ± 6.9	101.4 ± 3.8	84.8 ± 4.5*	78.7 ± 3.0*	82.8 ± 3.2*
Infarct scar/risk (%)	43.8 ± 5.2	80.0 ± 2.9	55.8 ± 5.4	42.1 ± 8.1	83.8 ± 1.2	56.0 ± 7.2
Risk/LV mass (%)	13.2 ± 1.5	7.4 ± 0.9	11.3 ± 1.2	12.6 ± 1.7	8.9 ± 1.5	11.3 ± 1.3
Infarct/LV mass (%)	5.7 ± 0.8	5.9 ± 0.7	5.8 ± 0.6	5.0 ± 0.9	7.5 ± 1.3	5.9 ± 0.8
Transmurality of scar (%)	85 ± 4	100 ± 0†	90 ± 4	86 ± 5	100 ± 0	91 ± 4
Hydroxyproline (mg/g)						
Normal zone	4.8 ± 0.3	5.1 ± 0.1	4.9 ± 0.2	4.7 ± 0.3	5.3 ± 0.3	4.9 ± 0.2
Infarct zone	50.5 ± 4.5‡	45.1 ± 7.8‡	48.4 ± 4.1‡	39.0 ± 6.2‡	56.3 ± 4.5‡	44.8 ± 4.7‡

*$p < 0.009$, digoxin versus control group or subgroup. †$p < 0.05$, collateral ligation (CL) versus no collateral ligation subgroups. ‡$p < 0.001$, infarct zone versus normal zone within group. LV = left ventricular.

short-axis plane ($p < 0.025$) and at the apex ($p < 0.001$) and less noninfarct wall thickness ($p < 0.0025$).

Hemodynamic changes. Peak positive left ventricular dP/dt was higher with inotropic stimulation, but heart rate, mean left atrial pressure and mean blood pressure were similar in the two groups (Table 3). Peak negative dP/dt was similar at baseline (1,169 vs. 1,187 mm Hg/s, p = NS) but was higher in the digoxin group at 1 week (1,268 vs. 1,087 mm Hg/s, $p < 0.05$) and 6 weeks (1,275 vs. 1,008 mm Hg/s, $p < 0.05$). Electrocardiograms showed a predominant sinus rhythm and no difference in frequency of Q waves or ventricular and supraventricular arrhythmias between groups or corresponding subgroups.

Infarct wall systolic thinning and diastolic bulging in vivo. For all 36 dogs, systolic thickening averaged 29 ± 3% in the noninfarct wall and 31 ± 2% in the infarct wall before occlusion and 29 ± 3% in the noninfarct wall at 2 days after occlusion, with no difference between groups. At 2 days, systolic thinning of the infarct wall was similar in both groups (−4 ± 1% vs. −7 ± 2%, p = NS). However, compared with the control group, systolic thickening of the noninfarct wall and systolic thinning of the infarct wall increased in the digoxin group between 2 days and 6 weeks (Fig. 1). Digoxin also produced more diastolic bulging of the infarct wall between 1 and 3 weeks (Fig. 1). Diastolic areas were similar in the two groups at the papillary level but larger ($p \leq 0.05$) at the apex with digoxin. At 6 weeks, ventricular aneurysms were more frequent with digoxin (17 of 18 vs. 9 of 18, chi-square 6.78, $p < 0.005$). The structural diastolic bulge with digoxin was greater both at postmortem examination and in vivo (Fig. 2).

Diastolic infarct wall stretch and thinning in vivo. Preocclusion values of anterior (7.9 vs. 7.8 cm) and posterior (4.3 vs. 4.4 cm) segment lengths and expansion indexes (1.86 vs. 1.79) were similar for the digoxin and control groups (Fig. 3). Digoxin produced a slightly greater increase in the infarct-containing anterior segment length and expansion index between 2 and 6 weeks than that in the control group, but no significant change was seen in the non–infarct-containing posterior segment length. Digoxin also produced a marked decrease in infarct wall thickness and thinning ratio between 2 and 6 weeks but a modest decrease in normal wall thickness (Fig. 3). At 6 weeks, the digoxin group had significantly less infarct wall thickness (3.7 ± 0.1 vs. 5.0 ± 0.3 mm, $p < 0.001$), a lower thinning ratio (0.39 ± 0.01 vs. 0.51 ± 0.03, $p < 0.001$)

Table 2. Infarct Scar Topography (mean ± SEM)

	Control Group			Digoxin Group		
	No CL	CL	All	No CL	CL	All
Short-axis map (low papillary)						
Extent of infarct scar (degrees)	104 ± 10	156 ± 21	121 ± 11	152 ± 11*	175 ± 14	160 ± 9*
Infarct wall thickness (mm)	7.3 ± 0.7	6.7 ± 0.9	7.1 ± 0.6	6.2 ± 0.3	4.8 ± 0.6	5.7 ± 0.3*
Noninfarct wall thickness (mm)	14.7 ± 0.5	15.0 ± 0.7	14.9 ± 0.4	13.2 ± 0.2*	13.8 ± 0.2	13.4 ± 0.2*
Area of infarct scar (cm^2)	1.9 ± 0.2	2.3 ± 0.3	2.0 ± 0.2	1.8 ± 0.2	2.0 ± 0.1	1.9 ± 0.2
LV cavity area (cm^2)	2.7 ± 0.3	3.5 ± 0.3	3.2 ± 0.3	1.8 ± 0.2*	1.9 ± 0.2*	1.8 ± 0.2*
Long-axis map (radiographs)						
Apical wall thickness (mm)	3.7 ± 0.3	2.8 ± 0.3	3.4 ± 0.2	2.6 ± 0.1*	1.8 ± 0.1*	2.3 ± 0.1*
Depth of endocardial bulge (mm)	5.2 ± 0.6	6.1 ± 1.1	5.8 ± 0.8	8.7 ± 0.8*	10.3 ± 2.3	9.2 ± 0.9*
Depth of epicardial bulge (mm)	2.2 ± 0.7	5.2 ± 2.1	2.8 ± 0.8	3.4 ± 0.3	6.7 ± 1.1	4.5 ± 0.5*

*$p < 0.05$, digoxin versus and control groups or subgroups. Abbreviations as in Table 1.

Table 3. Hemodynamic Variables in Control and Digoxin Groups (mean ± SEM)

Time	Heart Rate (beats/min)		Mean Left Atrial Pressure (mm Hg)		Mean Arterial Pressure (mm Hg)		Peak dP/dt (mm Hg/s)	
	Control Group	Digoxin Group	Control Group	Digoxin Group	Control Group	Digoxin Group	Control Group	Digoxin Group
Before ligation	86 ± 3	84 ± 3	6 ± 0	6 ± 0	110 ± 2	102 ± 3	1,225 ± 25	1,244 ± 58
Day 2	97 ± 2*	89 ± 3	16 ± 1*	14 ± 1*	110 ± 3	105 ± 2		
1 wk	96 ± 3	90 ± 3	14 ± 1*	13 ± 1	105 ± 4*	105 ± 3	1,230 ± 75	2,239 ± 57†
2 wk	106 ± 5*	110 ± 5*	14 ± 2	13 ± 1	103 ± 3	99 ± 3		
3 wk	102 ± 4	100 ± 4*	14 ± 2	13 ± 1	103 ± 2	100 ± 2	1,173 ± 64	2,398 ± 162†
4 wk	96 ± 5*	96 ± 5*	13 ± 1	12 ± 1	102 ± 3	99 ± 2		
5 wk	94 ± 6	94 ± 5	14 ± 2	12 ± 1	104 ± 3	99 ± 2		
6 wk	101 ± 5	91 ± 5	13 ± 2	10 ± 1	105 ± 3	100 ± 2	1,046 ± 59	2,437 ± 69†

*$p < 0.001$, significance of difference versus preceding value within the group. †$p < 0.05$, significance of difference comparing corresponding values in digoxin and control groups. dP/dt = first derivative of left ventricular pressure.

and slightly less noninfarct wall thickness (9.4 vs. 9.9 mm, $p < 0.05$) than the control group.

Left ventricular volumes and function in vivo. Compared with the control group, the digoxin group had an increased extent of regional dysfunction but a limited progression of global dilation and preserved volume ejection fraction (Fig. 4). There was no asynergy in either group before occlusion. At 2 days after occlusion, circumferential asynergy was 25% (papillary level) and total asynergy 15% of the surface area for the 36 dogs, with no difference between groups. However, percent change in asynergy (between 2 days and 6 weeks) was greater in the digoxin group at the papillary level (22 ± 5% vs. 3 ± 7%, $p < 0.025$) and for the entire ventricle (21 ± 6 vs. −4 ± 5%, $p < 0.0005$) than in the control group. Left ventricular volumes in the digoxin and control groups were similar at baseline for end-diastole (60 vs. 57 ml) and end-systole (25 vs. 22 ml). However, percent increases between 2 days and 6 weeks were lower with digoxin for diastolic volume (13 ± 6% vs. 36 ± 8%, $p < 0.01$), systolic volume (6 ± 7% vs. 33 ± 10%, $p < 0.01$) and diastolic endocardial surface area (4 ± 3% vs. 29 ± 7%, $p < 0.0025$). Left ventricular ejection fractions in the two groups were similar at 2 days (43% vs. 44%) and 6 weeks (48% vs. 46%).

In vivo left ventricular mass. Digoxin limited the increase in left ventricular mass seen in the control group (Fig. 5). Ventricular mass was similar in the two groups at baseline

Figure 1. In vivo changes in systolic thickening and regional bulging at the papillary level. D = day; PO = preocclusion; W = week.

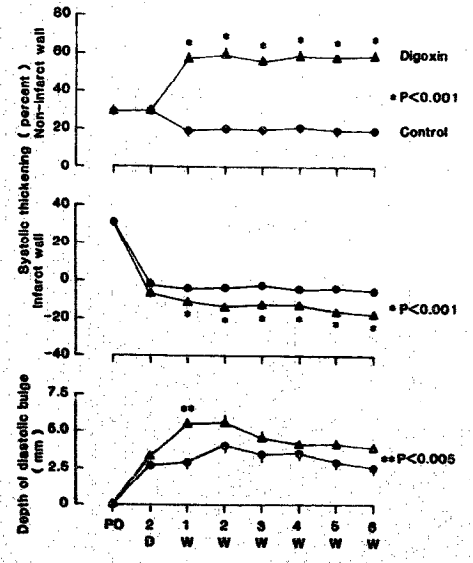
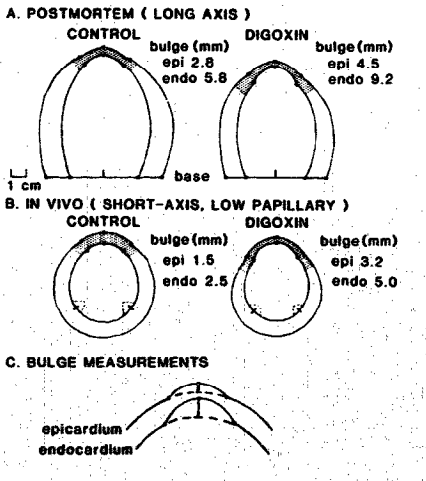


Figure 2. Epicardial (epi) and endocardial (endo) bulging. Average maps at 6 weeks show the diastolic bulge. **A,** Postmortem (long-axis radiographs). **B,** In vivo (short-axis echocardiograms). **C,** Measurements of the bulge. **Dots** = landmarks for measuring bulging; **shading** = scar or asynergy; **dashed lines** = extrapolated contour (4); **arrows** = depth of bulge.



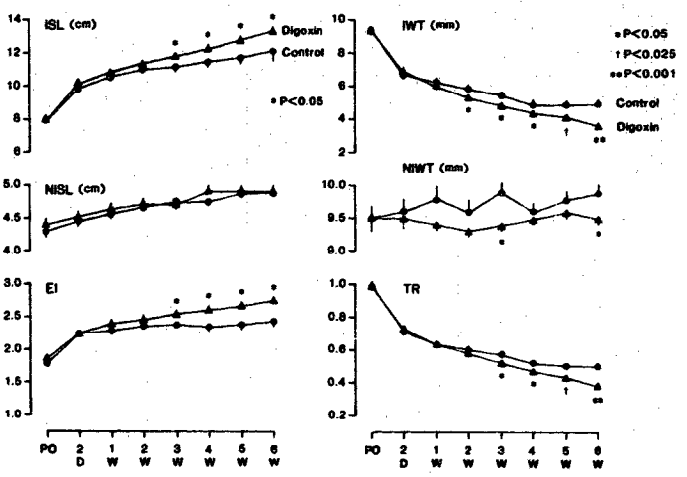


Figure 3. In vivo changes in infarct wall expansion **(left panel)** and thinning **(right panel)** at the papillary level. EI = expansion index; ISL = infarct-containing segment length; IWT = infarct wall thickness; NISL = non-infarct-containing segment length; NIWT = noninfarct wall thickness; TR = thinning ratio; other abbreviations as in Figure 1.

(79 vs. 85 g) but less with digoxin between 1 week (86 ± 3 vs. 99 ± 5 g, $p < 0.01$) and 6 weeks (86 ± 3 vs. 107 ± 4 g, $p < 0.001$). In vivo left ventricular mass at 6 weeks showed good correlation with postmortem mass of the formalin-fixed ventricles at 6 weeks ($r = 0.81$, $p < 0.001$).

Infarct transmurality and in vivo effects of inotropic stimulation. Because infarct transmurality was 100% in 12 dogs with collateral ligation (6 in each group) and 85% (range 50% to 90%) in the other 24 dogs (Table 1), we compared in vivo remodeling in those subgroups (Fig. 6). There was consistently more infarct remodeling in the 100% transmurality subgroups with collateral ligation than the 85% transmurality ("nontransmural") subgroups without collateral ligation, and the effect of digoxin on infarct remodeling was more marked with 100% transmurality. At 6 weeks, diastolic bulging with digoxin was slightly greater (p = NS) in both transmural (3.0 vs. 2.4 mm) and nontransmural (2.8 vs. 2.6 mm) subgroups. Systolic bulging with digoxin was significantly greater ($p < 0.05$) in both subgroups (transmural: 4.3 ± 0.3 vs. 3.1 ± 0.3 mm; nontransmural: 3.9 ± 0.5 vs. 2.5 ± 0.6 mm). However, ejection fraction was preserved, and increase in mass was prevented in both digoxin subgroups.

Discussion

The principal new finding in the present study is that prolonged, positive inotropic stimulation with digoxin during healing after small anterior myocardial infarction in the dog increases expansion, bulging and thinning of the infarct area but limits global ventricular dilation and increase in ventricular mass and preserves systolic function. In addition, regional topographic deformation with digoxin was more marked in infarcts with 100% than 85% transmurality. However, inotropic stimulation with digoxin did not produce significant changes in heart rate, mean left atrial pressure (an index of preload) and mean arterial pressure (an index of afterload) and did not decrease infarct collagen content.

Potential mechanisms. The present findings suggest that increased force of contraction of the normal zone contributed to the preservation of global chamber size and function. In addition, prolonged increase in contractile pull of the normal segment in systole and systolic bulging most likely contributed to greater diastolic remodeling of the infarct area. The apparent lack of difference in stroke volume between groups (Fig. 4) suggests that the increase in stroke volume caused by the Starling mechanism in the control group with a larger diastolic volume was as effective as that resulting from augmented contractility in the digoxin group with a smaller diastolic volume. Furthermore, more systolic bulging and aneurysm with inotropic stimulation might have resulted in more wasted stroke volume. Apparent linkage between systolic and diastolic shape deformation with inotropic stimulation could be explained by an increase in systolic twist and diastolic untwist (12,13). Thus, in the normal ventricle, potential energy stored by straining the intercellular collagen matrix (14–17) during twist is released during untwist. In the infarcted ventricle, remodeling of the collagen matrix with rupture of intermyocyte struts (6,18,19) leads to myocyte slippage (20,21), regional diastolic bulging, altered curvature and regional differences in twist and untwist. By increasing the twist and untwist of noninfarcted myocardium, inotropic stimulation could therefore increase the pull on the infarct zone in systole and diastole (12). Because diastolic untwist is inversely related to end-systolic volume (12), the smaller systolic volumes and increased peak negative dP/dt with digoxin in the present study probably contributed to increasing untwist. Increase in twist and untwist during infarct healing could also promote strut rupture and myocyte slippage in the infarct zone. The report

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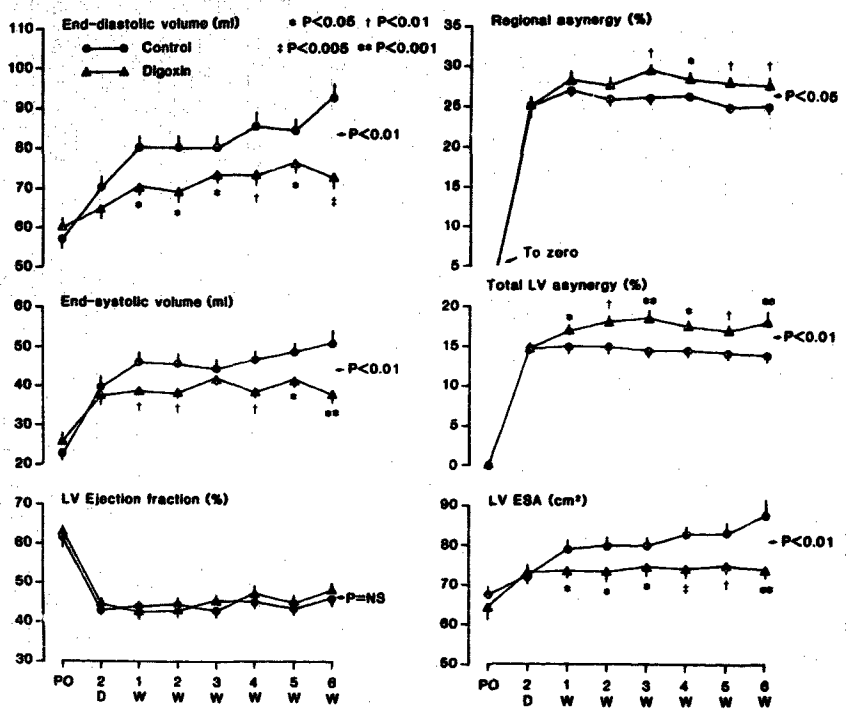


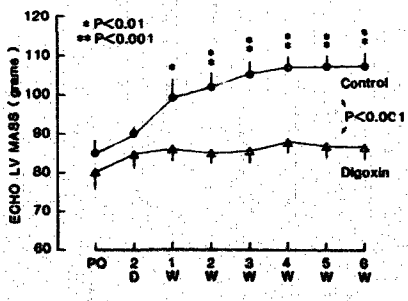
Figure 4. In vivo changes in ventricular volumes, ejection fraction (**left panel**), asynergy and surface area (**right panel**). ESA = endocardial surface area; LV = left ventricular; other abbreviations as in Figure 1. Arrows indicate p value for difference between plots.

that myocyte disarray at scar borders of healed infarcts interferes with mechanical coupling and contributes to dysfunction (22) suggests that in later stages of healing, augmented inotropism could improve mechanical coupling and function at scar borders and increase pull on the scar.

Diastolic bulging and global ventricular dilation. The findings in our control group are consistent with the concept that more early diastolic bulging leads to more global ventricular dilation (1–4). Prolonged inotropic stimulation resulted in a dissociation of this relation between regional and global left ventricular dilation. Thus, increased diastolic bulging in the digoxin group was associated with very little increase in systolic or diastolic volumes. In fact, both volumes were lower than those in the control group. This dissociation can be explained on the basis of a combination of increased systolic shortening (secondary to increased positive inotropism) and an augmentation of the normal Frank-Starling response to increased end-diastolic length. Volume overload in our control group was associated with an increase in ventricular mass, and smaller volumes in the inotrope group showed no increase in mass. These findings are consistent with the concept of less stretch → less stress → less hypertrophy.

Inotropic stimulation with digoxin. In the present study, we used digoxin, a class II inotrope (8), to augment contractility. The dogs in the digoxin group showed no evidence of toxicity, vasoconstriction, conduction abnormalities, increased arrhythmias or increased mortality. The observed increase in dP/dt was similar to that reported in dogs given digoxin after anterior infarction (23) and in normal dogs given another

Figure 5. In vivo changes in ventricular mass. Echo = echocardiographic; other abbreviations as in Figures 1 and 4. Arrows indicate p value for difference between plots.



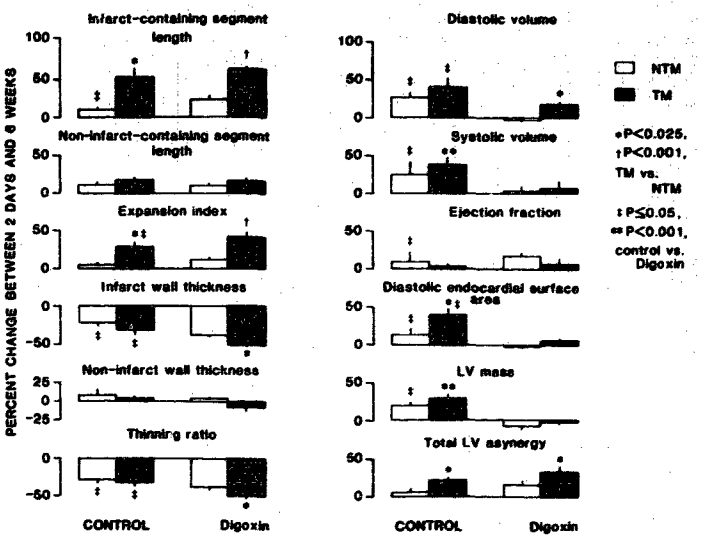


Figure 6. Effect of transmurality on regional **(left panel)** and global **(right panel)** topographic variables. LV = left ventricular; NTM = nontransmural or 85% transmurality; TM = transmural or 100% transmurality.

inotrope, such as dobutamine (13). The hemodynamic changes seen with digoxin were also in agreement with other reports (10,23). The use of digoxin after infarction remains controversial. Clinical studies claiming that digoxin is harmful in infarction and increases mortality (24,25) have been challenged (26). The present study focused on the effect of inotropic stimulation during postinfarction healing and was not designed to evaluate the efficacy of postinfarction digoxin therapy.

Other studies. In all studies, cardiac glycosides improved systolic function in noninfarct zones but the effects on infarct zones have been variable, depending on timing and infarct size. In conscious dogs with myocardial ischemia, ouabain given acutely produced global positive inotropic effects, increased systolic shortening in normal segments and restored shortening in akinetic segments (27). In conscious dogs with infarction, acutely administered acetylstrophanthidin produced hemodynamic benefit on day 7 but not on day 1 (28). In anesthetized dogs with infarction, acute digoxin increased tension markedly in normal and border zones but only slightly in the ischemic zone (29). In patients with acute infarction, acutely administered digoxin increased contractility in noninfarct zones and aneurysmal bulging in infarct zones (30), in agreement with our study. In a study of ventricular aneurysm after a first infarction, more patients had received digoxin (31). However, in a recent study (32) comparing the prolonged effects of digoxin and captopril (begun 7 to 10 days after infarction and continued for 1 year) in patients with a large anterior infarction and severe ventricular dysfunction, digoxin increased systolic and diastolic volumes and ejection fraction without altering wall motion indexes. In that study, there was no placebo group, and regional bulging was not measured. Although digoxin prevented hypertrophy in rat models of prolonged pressure overload (33,34), there are no controlled data on the effects of prolonged inotrope or digoxin on postinfarction hypertrophy.

Infarct size, collagen content and regional bulging. Increased inotropism did not appear to extend infarct size in our study. Ventricular asynergy at 2 days, which reflects infarct size (11), and postmortem infarct scar sizes at 6 weeks were similar in the digoxin and control groups. In dog models, inotropic stimulation with digoxin during acute infarction increases myocardial oxygen demand and ischemic injury in nonfailing ventricles (35), reduces ischemic injury in failing hearts (36), increases ventricular contractility without extending necrosis (23), increases reperfusion injury and decreases perfusion (37). In our study, where digoxin was begun 2 days after acute infarction, we cannot exclude the possibility that digoxin might have increased myocardial oxygen demand and decreased perfusion of the healing infarct, thereby promoting ischemia, collagen matrix damage and bulging (16). Several postmortem studies (38–42) have emphasized that collagen contributes to tensile strength of the infarcted ventricle and scar. For example, high intraventricular pressures are needed to stretch or disrupt coiled perimysial fibers in normal rat ventricles (41). Because digoxin did not alter infarct collagen content at 6 weeks in our study, it seems unlikely that decreased deposition or increased removal of infarct collagen played a significant role in increasing regional bulging. However, changes in collagen type or architecture cannot be excluded. New infarct collagen that is deposited during early healing is mostly immature, and mature collagen production does not begin until 7 to 14 days in the dog (43). Immature and type III collagen are weaker than mature and type I collagen (15,22). Although collagen maturity and type I collagen in dog infarct scars increase by 6 weeks (22), 15-week rabbit infarct scars are still susceptible to irreversible strain (44). In the present study,

the finding that in vivo diastolic bulging was declining in both groups at 6 weeks suggests that further scar remodeling can occur with inotropic stimulation after 6 weeks but is likely to be minor. The finding that mature collagen cross-linking in the 13-week rat infarct scar exceeds that in noninfarcted myocardium (45) supports this view.

Study limitations. We used a model of small anterior infarctions to increase the probability of survival over 6 weeks so that remodeling in the same animals could be studied. The infarcts in this model shrink from ~20% on day 1 to ~10% at 6 weeks (5). It is possible that prolonged inotropic stimulation during healing after larger anterior transmural infarctions, which have more infarct collagen matrix disruption (6) and more aneurysmal bulging and global dilation (4,6), might produce more ventricular dilation and still preserve function, as suggested in clinical studies (33).

Clinical implications. The overall results suggest that final outcome of prolonged inotropic stimulation involves a balance of effects on the infarcted and noninfarcted regions. In small anterior infarcts, inotropic stimulation with digoxin increases regional bulging, but infarct collagen content, ventricular size, mass and function are preserved. The effect of inotropic stimulation was more marked in the more transmural infarcts. Our findings are clinically pertinent to postinfarction survivors in the thrombolytic era who might require therapy with inotropic agents.

Conclusions. Prolonged inotropic stimulation during healing after small anterior infarction increases regional bulging without decreasing infarct collagen content and preserves ventricular size, mass and function.

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