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Reversal of Dysfunction in Postischemic Stunned Myocardium by Epinephrine and Postextrasystolic Potentiation

LEWIS C. BECKER, MD, JOSEPH H. LEVINE, MD, ANTHONY F. DiPAULA, BA, THOMAS GUARNIERI, MD, THOMAS AVERSANO, MD

Baltimore, Maryland

After brief coronary occlusions, myocardium may become "stunned," exhibiting prolonged depression of function despite the absence of necrosis. Because of the accompanying decline in adenosine triphosphate and adenine nucleotide precursors, a deficiency of energy supply has been proposed as the basis for postischemic dysfunction. This study examined whether sufficient functional and metabolic reserve exists in stunned myocardium to sustain a prolonged, maximal inotropic response to epinephrine and postextrasystolic potentiation. In 11 open chest dogs, the left anterior descending coronary artery was occluded for 5 minutes, followed by 10 minutes of reflow, repeated 12 times, with a final 1 hour recovery period. Regional myocardial function was measured using pairs of ultrasonic dimension crystals implanted in ischemic and nonischemic zones.

During repetitive reflows a progressive decrease in mean systolic segment shortening occurred: baseline 21.8%, 1st reflow 15.2%, 12th reflow 4.3%, 1 hour recovery 7.9%. Intravenous epinephrine, titrated to produce a maximal inotropic response, caused segment shortening to increase to 21.6% after 10 minutes and to 24.8% after 1 hour of infusion, despite a 20 mm Hg increase in systolic pressure. The same dose of epinephrine given before ischemia increased segment shortening to 30.5%. In six of the dogs, postextrasystolic potentiation before ischemia increased segment shortening from 21.8 to 31.1%, and after 1 hour of recovery from ischemia, from 7.9 to 24.8%. Lesser increases in segment shortening were also seen in nonischemic segments.

The results indicate that stunned myocardium possesses considerable functional reserve. Deficient energy stores are therefore not likely to be the basis for depressed function seen at rest in stunned myocardium.

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Although coronary reperfusion has been shown to anatomically salvage ischemic myocardium, function may remain depressed, even in the absence of infarction, for hours or days after normal flow is restored (1–4). Salvaged myocardium demonstrating a prolonged impairment of function after ischemia has been referred to as "stunned" (4,5). Despite reduced rest function, administration of catecholamines has been shown to produce at least a short-term functional improvement in stunned myocardium in animal studies (6,7). However, many questions remain unanswered about the response of the stunned myocardium to inotropic stimuli: 1) Is the inotropic response of the stunned myocardium quantitatively normal, that is, equal to the improvement seen with the same inotropic stimulus before ischemia? 2) Can a normal maximal contractile response be attained? 3) Is the inotropic response dependent on beta-adrenergic receptor activation? 4) Can the response be sustained during prolonged inotropic stimulation?

Several studies (4,5,8,9) have shown that a brief ischemic insult, insufficient to produce myocardial necrosis, leads to a depletion of tissue adenine nucleotides, and that these compounds are replaced slowly with a time course similar to the recovery of function. It has therefore been postulated (5) that dysfunction in stunned myocardium may be caused by a deficiency of adenosine triphosphate and high energy phosphate precursors. If this hypothesis is correct: 1) catecholamines should produce only a transient improvement in function, which would ultimately be limited by the reduced high energy reserves of the myocardial cells, and 2) the maximal contractile reserve of the stunned myocardium should be reduced. Although earlier studies have

From the Cardiology Division, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland. This study was supported by the Specialized Center for Research in Ischemic Heart Disease Grant HL 17655 from the National Institutes of Health, Bethesda, Maryland. Drs. Levine and Aversano were recipients of National Research Service Award-Training Grant 5 T32 HL 07227 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

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Address for reprints: Lewis C Becker, MD, Division of Cardiology, The Johns Hopkins Hospital, 600 North Wolfe Street, Halsted 500, Baltimore, Maryland 21205.

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shown improved function of the stunned myocardium with dopamine (6,7), maximal inotropic stimulation may not have been achieved. Postextrasystolic potentiation can augment function in segments unresponsive to catecholamines (10,11) and should therefore be better for eliciting maximal contractile reserve.

The purpose of this study was to determine whether postischemic stunned myocardium could respond to a sustained infusion of catecholamines and to postextrasystolic potentiation, whether maximal contractile reserve, as determined by postextrasystolic potentiation, could be realized during the infusion and whether the increased oxygen demands associated with an increased inotropic state would be detrimental, leading to a deterioration in function after the infusion was discontinued.

Methods

Eleven mongrel dogs of both sexes (20 to 26.8 kg) were anesthetized with intravenous sodium thiamylal (12.5 mg/kg body weight) and intramuscular alpha-chloralose (100 mg/kg) in urethane, and ventilated with room air at a constant volume. After a left lateral thoracotomy, the lungs were retracted and the heart was exposed.

Experimental protocol. Two pairs of 5 MHz cylindrical piezoelectric ultrasonic crystals (0.06 inch outside diameter, 0.06 inch length, 0.015 inch thickness, Vernitron) were implanted in the anterior descending coronary artery territory and one control pair in the anterolateral-basal region within the circumflex artery territory. The crystals were implanted in the midwall of the left ventricle, 10 to 15 mm apart, and oriented parallel to the minor axis (12). Segment lengths were measured with a pulse transit sonomicrometer (model Sono-1-XB, James Davis Consultants). Left ventricular pressure was measured with a catheter tip pressure transducer (Millar), which was inserted through an implanted silicone rubber left atrial catheter, and advanced across the mitral valve. Bipolar atrial pacing was performed at twice diastolic threshold by way of pacing wires sewn to the left atrial appendage. Catheters were placed in the descending aorta for blood pressure measurement and withdrawal of microsphere reference samples, and in the left atrium for microsphere injections. Pressures, segment lengths and lead II of the electrocardiogram were recorded continuously on a direct writing recorder (Gould Brush 200) at paper speeds of 0.25 to 100 mm/s.

Intravenous epinephrine. A pneumatic occluder was placed around the proximal anterior descending coronary artery just distal to the first diagonal branch. Postischemic dysfunction was induced with twelve 5 minute occlusions alternating with 10 minute recovery periods. Epinephrine (7.8 to 64 μg/min) was infused intravenously in each dog during the baseline period and again 1 hour after the final coronary occlusion. The second infusion was maintained continuously for 60 minutes. For the first four animals epinephrine was given before occlusion in increasing doses until a maximal increase in shortening was observed or until arrhythmias appeared. An attempt to use the same dose after ischemia in these four dogs was prevented by epinephrine-induced ventricular arrhythmias. The doses before and after ischemia in these four animals were as follows: 22 versus 16.8 μg/min, 16.4 versus 12.4 μg/min, 64 versus 44 μg/min at 10 minutes and 32.8 μg/min at 60 minutes and 11 versus 11 μg/min at 10 minutes and 7.8 μg/min at 60 minutes. In the last animal, ventricular fibrillation requiring two direct current shocks occurred between the 10 and 60 minute infusion measurements. For the remaining seven animals, a dose-response curve for epinephrine was constructed before ischemia. After ischemia, epinephrine was given in a dose to maximize shortening without arrhythmias. Measurements obtained before ischemia at the same epinephrine dose were then selected for comparison. For all dogs the mean dose was 24.5 μg/min before ischemia and 20.6 μg/min after ischemia at the 60 minute infusion time.

Postextrasystolic potentiation. This was performed during atrial pacing, both before and during epinephrine infusion, in 6 of the 11 animals using programmed atrial stimulation, by scanning atrial diastole until the refractory period of the atrium or atrioventricular (AV) node was reached. A compensatory pause ($2 \times A_1A_1 - A_1A_2$) was programmed (Bloom) after each premature interval. Atrial rather than ventricular stimulation was performed to maintain atrial contraction during postextrasystolic potentiation measurements. The hemodynamic response to postextrasystolic potentiation used in our results was the response to the shortest A_1A_2 interval that did not result in AV block or arrhythmias. In four of the six animals, the A_1A_2 interval was limited by atrial or ventricular arrhythmias, or both, while in one it was limited by AV block.

Measurements of segment shortening and segment length. Signals from the ultrasonic crystals, left ventricular pressure and left ventricular first derivative of pressure (dP/dt) were also routed to a microcomputer (North-Star Horizon) at selected times during the experiment, digitized at 150 Hz by a Tecmar 12 bit analog to digital converter and recorded on floppy disk for later computerized analysis. Percent systolic segment shortening was calculated as segment shortening (end-diastolic minus end-systolic length) divided by end-diastolic segment length times 100, and represented the average of at least five heartbeats. The end-systolic segment length was measured 20 ms before peak negative left ventricular dP/dt (13); end-diastolic length was measured just before the onset of positive left ventricular dP/dt. One of the two crystal pairs in the left anterior descending artery territory in each dog was chosen to represent the ischemic zone. This selection was based on 1) the maintenance of signal throughout the experiment, 2) the absence of necrosis

in the region of the crystals, 3) the adequacy of the baseline measurement, and 4) the adequacy of the baseline response to epinephrine.

Measurement of myocardial blood flow. Blood flow to ischemic and normal myocardium was determined by radioactive microspheres (15 μm diameter, New England Nuclear Co.), labeled with cesium-141, tin-113, ruthenium-103, niobium-95 or scandium-46, and injected into the left atrium. Three to five million microspheres were injected after a 3 minute mechanical agitation, while reference arterial samples were withdrawn at a constant rate of 2.16 ml/min by a calibrated pump. Blood flow was calculated from the radioactivity in tissue and reference blood samples using standard methods after correction for overlap of the different radionuclides. In each dog, flows to ischemic and normal zones represented measurements in single tissue blocks weighing 1 to 3 g, divided into endocardial and epicardial halves and encompassing each crystal pair. Flows were obtained at baseline, during the first coronary occlusion and 60 minutes after the last ischemic episode; measurements were technically adequate in 10 of the 11 animals.

Hemodynamic and ultrasonic crystal measurements were made at end-expiration during the following periods: the baseline state, during the baseline epinephrine infusion, at the end of each occlusion and reflow period, 1 hour after the final occlusion, 10 and 60 minutes after the start of the postischemic epinephrine infusion and 20 minutes after termination of the infusion. In the six dogs in which postextrasystolic potentiation was performed, hemodynamic and ultrasonic crystal measurements were also made during postextrasystolic potentiation at the following times: the baseline state, baseline state plus epinephrine, 1 hour after the final coronary occlusion and during the end of the postischemic epinephrine infusion.

Myocardial tissue preparation. After this protocol, the animals were killed by intraatrial injection of potassium chloride. The hearts were cut into five to six short-axis slices from apex to base, each of which was incubated at 37°C in triphenyltetrazolium chloride for 20 minutes and photographed in color (14). The site of each ultrasonic crystal pair was marked with a needle for photography. After this, the site of each crystal pair was excised, weighed and counted for radioactivity for measurement of blood flow. The fresh tissue and photographs were both inspected to identify unstained areas which represented myocardial necrosis.

Statistical analysis. Data are presented as mean ± SEM. Sequential measurements were compared using a repeated measures analysis of variance (ANOVA). Statistically significant differences between selected means were confirmed using paired *t* tests.

Results

Effect of repetitive brief ischemic episodes. Systolic segment lengthening and an increase in end-diastolic segment length were noted in the left anterior descending artery territory during each occlusion, and the severity of these abnormalities was similar during the 1st and 12th occlusions (Table 1). The segmental wall motion abnormality recovered partially during each recovery period, but not back

Table 1. Systolic Shortening and End-Diastolic Length in Ischemic and Nonischemic Segments (11 dogs)

	Systolic Shortening (%)		End-Diastolic Length (mm)	
	Ischemic	Nonischemic	Ischemic	Nonischemic
Baseline	21.8 ± 1.2	14.5 ± 1.5	11.8 ± 0.5	13.6 ± 1.1
Epinephrine	30.5 ± 1.6‡	22.1 ± 1.7‡	12.1 ± 0.5	13.8 ± 1.2
Occlusion 1	−4.8 ± 2.7‡	17.5 ± 1.6	13.2 ± 0.5‡	14.1 ± 1.2*
Reflow 1	15.2 ± 2.9*	13.5 ± 1.5	12.0 ± 0.4	13.5 ± 1.2
Reflow 6	9.1 ± 2.7‡	11.4 ± 1.1*	12.2 ± 0.5	13.6 ± 1.2
Occlusion 12	−8.7 ± 1.0‡	14.0 ± 1.3	13.6 ± 0.5‡	14.3 ± 1.3‡
Reflow 12	4.2 ± 2.7‡	11.7 ± 1.0*	12.5 ± 0.6	13.8 ± 1.3
Postischemic recovery period (60 minutes)	7.9 ± 2.6‡	12.3 ± 1.1	12.3 ± 0.5	13.7 ± 1.3
Postischemic epinephrine (10 minutes)	21.6 ± 2.0†	16.7 ± 1.2†	12.0 ± 0.5	13.6 ± 1.3
Postischemic epinephrine (60 minutes)	24.8 ± 2.0†	17.0 ± 1.3†	12.0 ± 0.5	13.1 ± 1.4
Epinephrine discontinued (20 minutes)	16.6 ± 2.4	13.9 ± 0.7	12.2 ± 0.5	12.5 ± 1.4

*$p < 0.05$, ‡$p < 0.01$, compared with baseline; †$p < 0.01$ compared with postischemic recovery period.

to baseline. The residual dysfunction during sequential recovery periods was cumulative, resulting in severe postischemic dysfunction that was persistent during a 1 hour period after the last ischemic episode (Fig. 1). In the ischemic zone mean percent systolic shortening decreased from 21.8 ± 1.2 to 7.9 ± 2.6 ($p < 0.0001$) and end-diastolic length increased from 11.8 ± 0.5 to 12.3 ± 0.5 mm ($p = 0.15$). In addition, a delay in shortening was noted in all experiments after repetitive ischemia, with shortening occurring during early diastole coincident with the fall in left ventricular pressure (Fig. 2).

In contrast, in the nonischemic zone, a small and statistically insignificant increase in systolic shortening was seen during occlusion, and a modest decrease in shortening was seen during the 6th and 12th reflow periods, which returned to baseline after 60 minutes. Shortening during the 12th occlusion was also slightly less than shortening during the 1st occlusion. End-diastolic segment length increased during occlusion but was unchanged from baseline during all reflow periods (Table 1).

Hemodynamics. Heart rate decreased during the course of the experiment, falling from 132 beats/min at baseline to 119 beats/min 60 minutes after the last ischemic period ($p < 0.05$) (Table 2). Systolic and diastolic aortic pressures both increased during the same time period (systolic, 103 to 120 mm Hg, $p < 0.05$; diastolic, 69 to 84 mm Hg, $p < 0.05$). However, most of the hemodynamic changes occurred after the first occlusion, so that the changes from the first reflow period to the final recovery period were not significant (heart rate, 123 to 119 beats/min; systolic pressure, 115 to 120 mm Hg; diastolic pressure, 81 to 84 mm Hg). Left ventricular end-diastolic pressure increased during coronary occlusion, but otherwise demonstrated no significant changes.

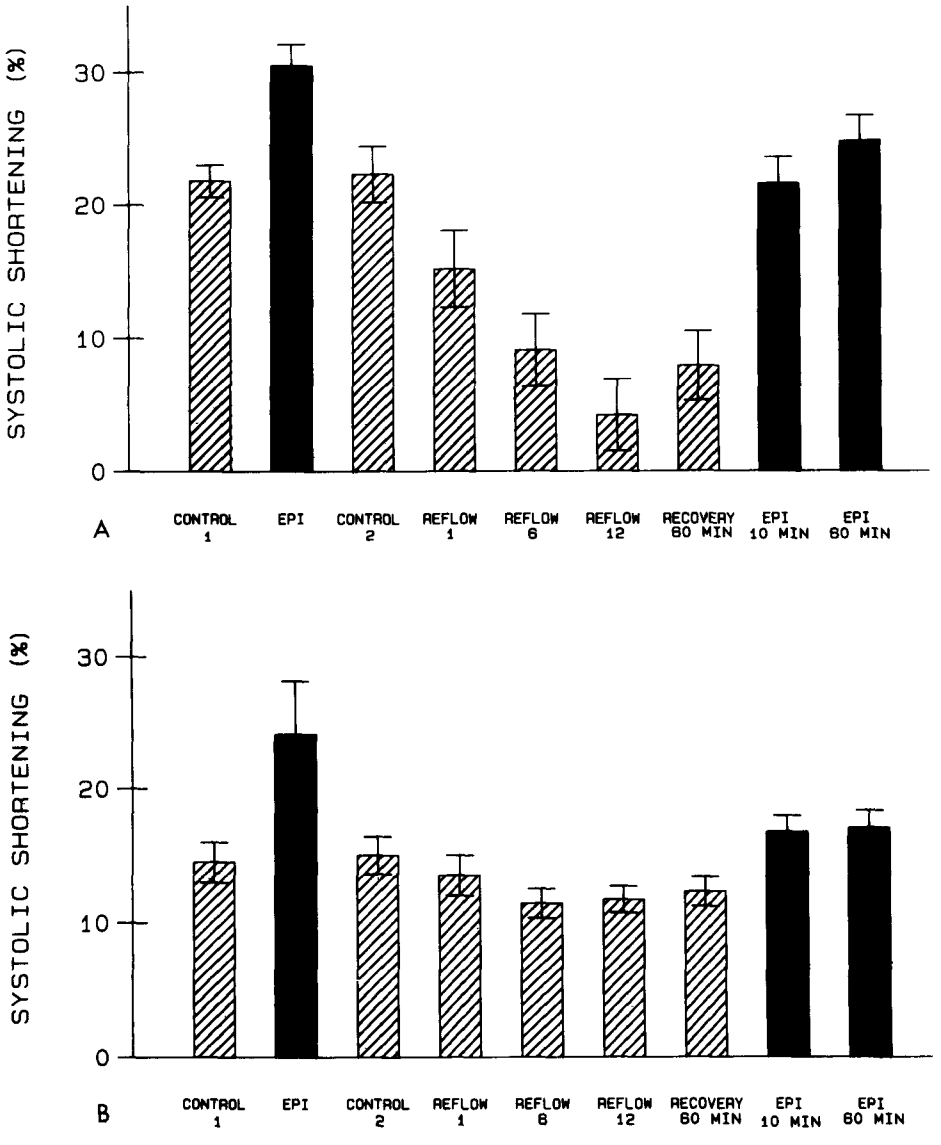

Figure 1. Percent systolic shortening in postischemic (**A**) and nonischemic (**B**) segments at selected times. **Black bars** indicate measurements during epinephrine (EPI). Note the progressive decrease in shortening in postischemic segments, minimal recovery over 60 minutes and marked increase in shortening during epinephrine, which is sustained for 60 minutes.

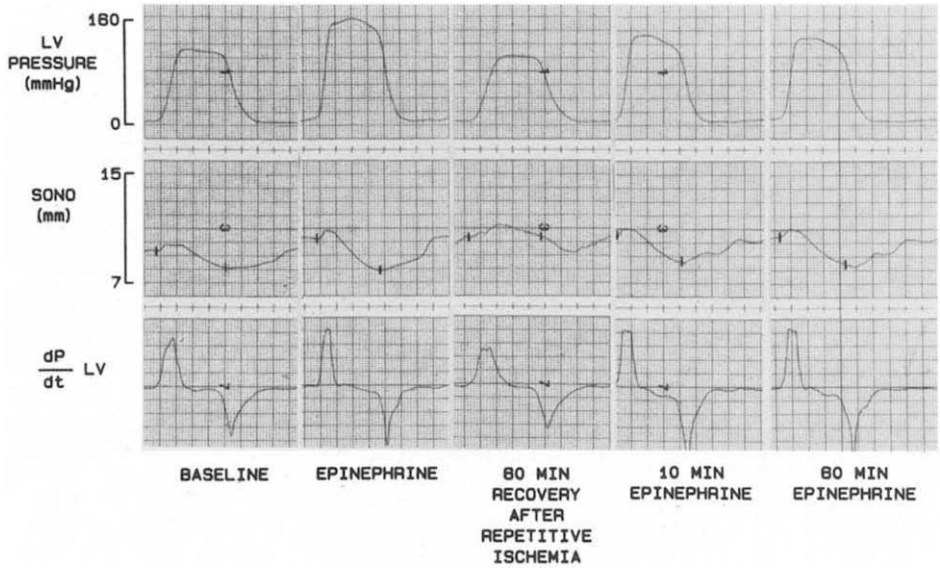

Figure 2. Segment length changes (SONO) from postischemic segment in a representative experiment. Short vertical lines on segment length tracing mark end-diastole and end-systole. Note markedly disordered left ventricular (LV) contraction during 60 minute recovery period, with systolic lengthening and early diastolic shortening. These abnormalities were reversed during epinephrine, despite rise in left ventricular systolic pressure.

Effect of catecholamine infusion. Epinephrine was infused intravenously during the baseline state and after the final 1 hour postischemic recovery period. During the baseline state, epinephrine led to an increase in percent systolic shortening but no change in end-diastolic length (Table 1). Systolic arterial blood pressure increased (103 to 125 mm Hg) but there were no significant changes in heart rate, diastolic arterial blood pressure or left ventricular end-diastolic pressure (Table 2).

After the 60 minute postischemic recovery period, intravenous epinephrine produced significant increases in percent systolic shortening in both ischemic and nonischemic zones (7.9 to 21.6% and 12.3 to 16.7%, respectively) (Table 1). End-diastolic segment length did not change significantly during the epinephrine infusion. The improvement in segment shortening was noted within a few minutes of the start of the catecholamine infusion and persisted without decrement during the entire 1 hour infusion period. Mean aortic systolic pressure increased from 120 to 140 mm Hg ($p < 0.05$) during the postischemic epinephrine infusion, but no significant changes occurred in aortic diastolic pressure, heart rate or end-diastolic pressure (Table 2). During the infusion, regional function in the ischemic zone recovered to above baseline values, although function in both the control and ischemic zones did not return to the level achieved with epinephrine before ischemia (Table 1). In the post-

Table 2. Hemodynamic Values in 11 Dogs

	HR (beats/min)	AoSP (mm Hg)	AoDP (mm Hg)	LVEDP (mm Hg)
Baseline	132 ± 6	103 ± 3	69 ± 3	7.2 ± 0.9
Epinephrine	134 ± 8	125 ± 5*	74 ± 5	8.6 ± 0.9
Occlusion 1	118 ± 6	110 ± 3	76 ± 4	10.9 ± 3.9*
Reflow 1	123 ± 6	115 ± 4*	81 ± 4*	8 9 ± 0.8
Reflow 6	119 ± 5	119 ± 4*	87 ± 4*	8.5 ± 1.0
Occlusion 12	113 ± 6	119 ± 4*	86 ± 6*	11.3 ± 1.0*
Reflow 12	113 ± 7*	120 ± 3*	85 ± 4*	8.9 ± 0.8
Postischemic recovery period (60 minutes)	119 ± 8	120 ± 2*	84 ± 5*	8.7 ± 1.0
Postischemic epinephrine (10 minutes)	114 ± 8	140 ± 4*†	91 ± 6*	9.2 ± 0.9
Postischemic epinephrine (60 minutes)	119 ± 9	134 ± 3*†	84 ± 5*	9.5 ± 1.0
Epinephrine discontinued (20 minutes)	116 ± 8	110 ± 4	72 ± 3	9.7 ± 1.3
ANOVA	p = 0 011	p = 0.0004	p = 0.0007	p = 0.044

*$p < 0.05$ vs. baseline; †$p < 0.05$ vs. postischemic recovery period. ANOVA = repeated measures analysis of variance comparing baseline, reflow 1, reflow 6 and reflow 12; AoDP = aortic diastolic pressure; AoSP = aortic systolic pressure; HR = heart rate; LVEDP = left ventricular end-diastolic pressure

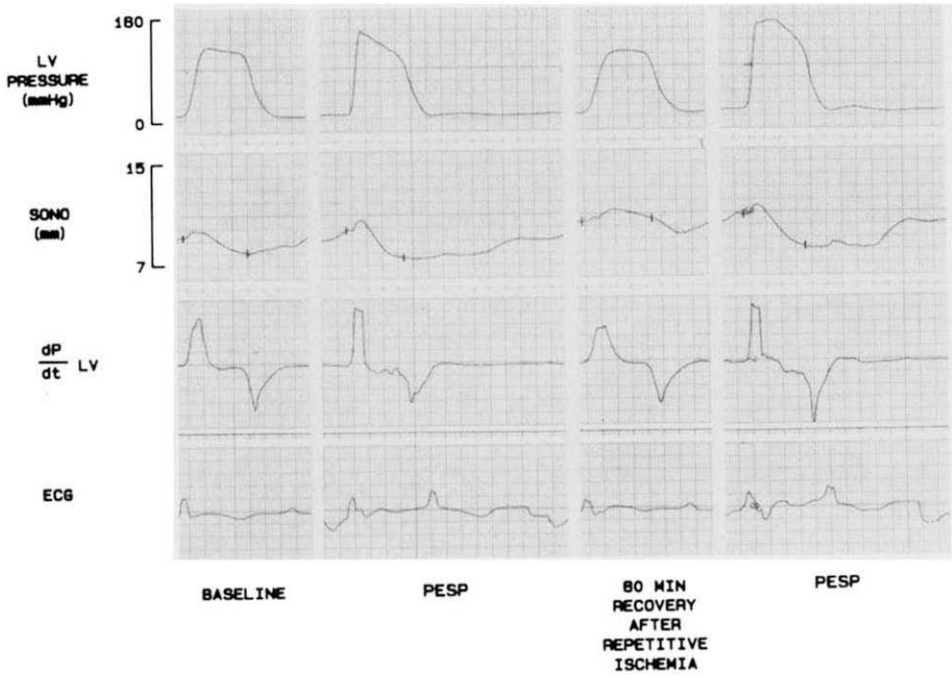

Figure 3. Segment length changes (SONO) during postextrasystolic potentiation (PESP) produced by atrial pacing. **Short vertical lines** on segment length tracing mark end-diastole and end-systole. Note marked improvement in systolic shortening during postextrasystolic potentiation. ECG = electrocardiogram.

ischemic segments mean percent systolic shortening reached 81% of the baseline epinephrine-stimulated value, compared with 77% in the nonischemic segments. Similar results were found in the first four animals, in which the postischemic epinephrine dose was slightly less than the preischemic dose, and in the next seven animals, in which the doses were identical (see Methods). In addition, the late systolic contraction in the ischemic zone disappeared during the epinephrine infusion (Fig. 2). The timing of shortening in the ischemic zone was altered so that peak shortening occurred in phase with the normal zone and was coincident with global left ventricular end-systole.

After termination of the infusion, impaired function returned in the ischemic zone (Table 2), but percent systolic shortening was no worse than during the 1 hour postischemic recovery period. Thus, the 1 hour epinephrine infusion led to a sustained improvement in regional myocardial function and was not associated with postinfusion depression of function over the 20 minute postinfusion observation period.

Effects of postextrasystolic potentiation. In order to determine the maximal contractile reserve of "stunned" myocardium, postextrasystolic potentiation was studied in 6 of the 11 animals. Postextrasystolic potentiation led to an improvement in segment function in each animal during control and postischemic conditions (Fig. 3). The increase in function seen with epinephrine was slightly less but not significantly different. The combination of epinephrine and postextrasystolic potentiation did not improve function more than either stimulus alone, either at baseline or after ischemia (Table 3). As with epinephrine, the increase in function

Table 3. Segment Shortening and End-Diastolic Length During Postextrasystolic Potentiation and Epinephrine

	Systolic Shortening (%)		End-Diastolic Length (mm)	
	Ischemic	Nonischemic	Ischemic	Nonischemic
Baseline	21.9 ± 1.5	13.0 ± 2.6	12.8 ± 0.6	11.4 ± 0.7
PESP	31.1 ± 1.7‡	23.8 ± 2.7‡	13.2 ± 0.6*	11.8 ± 0.6*
Epinephrine	28 5 ± 1 3*	20 7 ± 3.0*	12.8 ± 0.7	11 5 ± 0.6
Postischemic recovery period (60 minutes)	5.9 ± 3.4‡	11.6 ± 1.7	12.7 ± 0.9	11.0 ± 0.7
Postischemic PESP	24.8 ± 2 2†	19.7 ± 2 3†	12.5 ± 0.7	11.0 ± 0.7
Postischemic epinephrine (60 minutes)	22.5 ± 2 2†	15.6 ± 1 6	12.4 ± 1.0	10.9 ± 0.9
Postischemic epinephrine plus PESP	25.6 ± 1.9†	18.6 ± 3 2	12.6 ± 0.9	11 0 ± 0.4

*$p < 0.05$ vs. baseline, †$p < 0.01$ vs. postischemic recovery period; ‡$p < 0.01$ vs. baseline. PESP = postextrasystolic potentiation

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achieved with postextrasystolic potentiation after ischemia was less than that obtained at baseline. However, this finding was true of both ischemic and nonischemic segments (Fig. 4).

Regional myocardial blood flow. Regional myocardial blood flow was measured at baseline, during the first coronary occlusion and 60 minutes after the last occlusion (Table 4). During occlusion, flow decreased markedly in ischemic zone segments to about 6 to 8% of baseline but did not change significantly in nonischemic segments. During recovery, flow was mildly depressed in both endocardial and epicardial layers of the reperfused segments (0.92 versus 1.35 ml/min per g and 1.31 versus 1.78 ml/min per g, respectively), and was also somewhat reduced in the nonischemic segments (statistically significant only in the endocardium). At each time point, endocardial flow was significantly less than epicardial flow in ischemic segments but not in nonischemic segments.

Myocardial necrosis. In 9 of the 11 dogs, triphenyltetrazolium chloride staining showed no areas of necrosis. In one dog a small focal area of nonstaining was observed in a mid-left ventricular slice, and in an additional dog, an area of necrosis encompassed the apical pair of crystals implanted in the ischemic zone (segment lengths from this pair were not used in the analysis).

Discussion

Improved function of postischemic myocardium by inotropic stimulation. The major finding in this study was that systemic epinephrine and postextrasystolic potentiation both produced a striking improvement in myocardial function in postischemic stunned myocardium. A sustained benefit was demonstrated during a continuous infusion of epinephrine lasting 1 hour, and the potential detrimental effect of sustained inotropic stimulation in the setting of an isch-

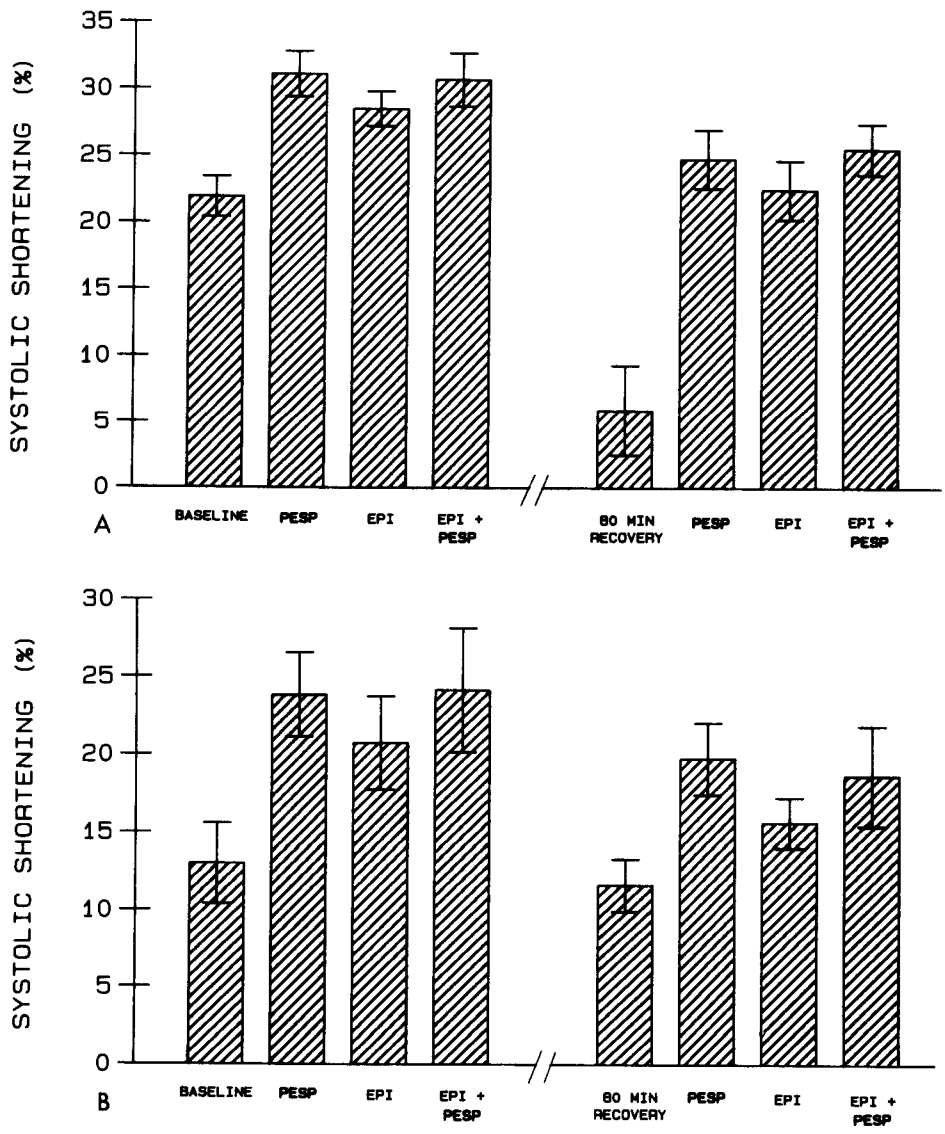

Figure 4. Percent systolic shortening in postischemic (**A**) and nonischemic (**B**) segments before (**left**) and after (**right**) ischemia. The differences between postextrasystolic potentiation (PESP), epinephrine (EPI) and epinephrine + postextrasystolic potentiation were not significant.

Table 4. Regional Myocardial Blood Flow

	Ischemic Zone (ml/g per min)		Nonischemic Zone (ml/g per min)	
	Endocardium	Epicardium	Endocardium	Epicardium
Baseline	1.35 ± 0.13	1.78 ± 0.22†	1.46 ± 0.16	1.54 ± 0.15
Occlusion 1	0.08 ± 0.03‡	0.14 ± 0.04†‡	1 34 ± 0 19	1.40 ± 0.14
Postischemic recovery period (60 minutes)	0.92 ± 0.08‡	1 31 ± 0.12*†	1.10 ± 0.13*	1.23 ± 0.13
ANOVA	$p < 0.001$	$p < 0.001$	$p < 0.05$	NS

*$p < 0.05$ vs. baseline; †$p < 0.02$ vs. corresponding endocardium; ‡$p < 0.01$ vs baseline.

emia-induced injury did not occur over the period of observation. Furthermore, maximal contractile reserve, as measured by postextrasystolic potentiation, was reached during pharmacologic inotropic stimulation in this model. The fact that epinephrine did not add to the augmentation of function by postextrasystolic potentiation supports the notion that the response to postextrasystolic potentiation reflected the true maximal contractile reserve of the myocardium.

Our results are in agreement with and extend the observations of Mercier et al. (6) and Ellis et al. (7). In those studies, postischemic dysfunction was transiently reversed with systemic dopamine. However, in the former study, no control zone was examined, while in the latter study, a 2 hour coronary occlusion was used, resulting in a mixture of necrotic and salvaged myocardium. In neither study was a sustained improvement in systolic function with catecholamines documented. Our results show that a functional response of the stunned myocardium to epinephrine can be maintained for at least 1 hour. Furthermore, the contractile reserve of the stunned myocardium appears to be "normal" relative to the response of the nonischemic segments. Although segment shortening during epinephrine or postextrasystolic potentiation, or both, was decreased in postischemic segments compared with baseline stimulated values, the same was true of segments that were never ischemic, and the fraction of the baseline response achieved was similar. The reduction in response after ischemia, occurring after 6 hours or more of anesthesia and open chest conditions, may have been due to anesthetic-induced myocardial depression or, perhaps more directly, to a rise in aortic systolic pressure with consequent increase in afterload.

Role of preload and afterload. The improvement in regional myocardial function seen with epinephrine was not due to changes in preload or afterload. Left ventricular end-diastolic segment length and pressure did not change significantly during the epinephrine infusion, but aortic pressure increased. Similarly, afterload was increased with postextrasystolic potentiation, although there was an associated increase in end-diastolic segment length during preischemia testing. After ischemia, end-diastolic segment length was unchanged with postextrasystolic potentiation, possibly resulting from a balance between the longer diastolic filling period and improved overall left ventricular function.

Role of beta-receptor stimulation. The finding that postextrasystolic potentiation and systemic epinephrine both caused a marked and quantitatively similar improvement in postischemic function suggests that beta-adrenergic receptor stimulation is not a necessary condition for this improvement. Although the final common pathway for both inotropic stimuli is believed to be an increase in intracellular calcium for troponin binding (15), catecholamines appear to interact with the myocardial beta-receptor to initiate an opening of calcium channels and release of calcium by the sarcoplasmic reticulum; the action of postextrasystolic potentiation, however, is thought to be independent of the beta-receptor (16).

Functional consequences of repeated, brief periods of ischemia. Our results indicate that repetitive brief periods of ischemia can lead to a cumulative impairment in myocardial function. Systolic shortening averaged 21.8% at baseline, 15.2% during reflow after the 1st occlusion, 9.1% after the 6th occlusion and 4.2% after the 12th occlusion. The finding of a cumulative functional deficit after repeated brief coronary occlusions has been a consistent one in our laboratory (17). In contrast, Weiner et al. (2) failed to show a cumulative impairment after three 20 minute occlusions alternated with 45 minute recovery periods. Lange et al. (18) demonstrated a slight but nonsignificant additional impairment in systolic function after two 5 minute occlusions separated by a 35 minute recovery period but no further decline in function after a third occlusion. In our study, the greatest increment of impairment was noted after the first occlusion and reflow period, but subsequent ischemic periods led to significant, although successively smaller effects. The cumulative deficit in our study could have been due to the accompanying increase in aortic pressure, but this explanation is unlikely because the major increase in pressure occurred during the first ischemic insult; the change between the 1st and 12th reflow periods was minimal and not statistically significant. The study of Geft et al. (19) showed that 14 to 18 repeated episodes of ischemia could produce necrosis, although a single episode was too brief. Small areas of subendocardial necrosis were seen in 7 of

24 dogs with repeated 15 minute coronary occlusions, 5 of 21 dogs with 10 minute occlusions and 3 of 32 dogs with 5 minute occlusions. Regional function was not assessed. It appears, therefore, that the number and duration of ischemic periods as well as the period of recovery may be important in determining the functional consequences of repeated, brief periods of ischemia. How directly our results can be extrapolated to single ischemic episodes is uncertain.

Myocardial viability. Myocardial viability in our study was documented using staining with triphenyltetrazolium chloride. Although the intermittent periods of reperfusion in this study appear to be protective, such staining cannot totally exclude myocardial necrosis, and it is possible that some degree of irreversible injury was produced. Fishbein et al. (14) showed that triphenyltetrazolium chloride can accurately indicate necrotic tissue if used 3 hours after coronary ligation, and Taylor et al. (20) found that the accuracy of triphenyltetrazolium chloride staining during the first hours after coronary occlusion is enhanced by reperfusion. More important, in an earlier study from our laboratory (17), using a similar repetitive ischemia/reflow protocol, electron microscopic observations revealed essentially normal ultrastructure in the postischemic segments.

Mechanism of impaired function in stunned myocardium. The mechanism by which systolic function is impaired in postischemic stunned myocardium is unknown. During ischemia, high energy phosphate production ceases and myocardial nucleotide and phosphocreatine pools are depleted (4,8,9,16). After reperfusion, phosphocreatine is quickly regenerated and often increases above baseline, but adenosine triphosphate and total adenine nucleotides may remain depressed for days. During ischemia, adenine nucleotides are converted to metabolites that diffuse freely across the sarcolemma and are lost from the myocyte. Repletion of adenosine triphosphate therefore requires new synthesis, a process that is much slower and more demanding of energy than the usual salvage pathways (21). It has been suggested (4,5,8), on the basis of these facts, that the impairment of function in postischemic stunned myocardium may be due to the depletion of adenosine triphosphate and purine precursors, and a lack of high energy phosphate reserves.

Our results do not support this hypothesis. Although rest function was depressed in stunned segments, a normal maximal inotropic response could be obtained with both postextrasystolic potentiation and epinephrine, and the response to epinephrine did not decline during 1 hour of continuous infusion. If energy production was the factor limiting function in stunned myocardium, the inotropic reserve should also have been depressed and the ability to sustain an increase in function should have been markedly curtailed (22). The finding of normal contractile reserve also suggests that the machinery for contraction is intact in the stunned myocardium.

Other possible mechanisms of impaired postischemic function have been proposed and include abnormalities in calcium handling by sarcoplasmic reticulum (23), alterations in left ventricular geometry producing increased regional loading, functional interruption of cardiac sympathetic nerves (24), abnormal regional electrophysiologic characteristics (25) and interruption of the creatine phosphate shuttle (26). The possible role of each of these factors in producing stunned myocardium awaits further study.

Clinical implications. Our findings may have important clinical implications. After reperfusion in the setting of an acute myocardial infarction, recovery of function in the salvaged myocardium may be delayed by hours or days. A more immediate assessment of the amount of salvage achieved may be possible by the measurement of regional inotropic reserve with catecholamine infusion or postextrasystolic potentiation. Such information may be important in deciding whether to perform coronary angioplasty on the infarct-related vessel. In patients with recurrent ischemia and severe depression of left ventricular function, catecholamines may be useful not only for circulatory support, but also for differentiation between infarcted and stunned viable regions; such differentiation may be important before deciding whether to proceed with revascularization.

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