Functional Characterization of Left Ventricular Segmental Responses during the Initial 24 h and 1 wk after Experimental Canine Myocardial Infarction

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ABSTRACT Characterization of the temporal evolution of resting segmental function and inotropic reserve after coronary occlusion may be important in evaluating attempts to salvage ischemic but nonnecrotic myocardium. Accordingly, we chronically implanted up to six pairs of pulse-transit piezoelectric crystals in the left ventricular myocardium of dogs to measure segmental wall thickness. Segments were separated into groups according to the loss of net systolic thickening (NET) at 5 min postocclusion of the left anterior descending coronary artery in awake, unsedated dogs. Group 1 included segments with NET values of 67–100+ (percent control); group 2 between 67 and 0; and group 3 <0 (paradoxical motion). 5 min after coronary occlusion, group 1 NET was 92±5% (SEM) although significant decreases occurred in NET in group 2 (36±4%) and group 3 segments (−33±5%). Between 5 min and 24 h after coronary occlusion, no further significant changes occurred in NET in groups 1, 2, and 3 crystals. Some segments underwent further functional deterioration between 24 h and 1 wk after left anterior descending coronary artery occlusion, although no overall change occurred in segments with mild to moderate ischemic dysfunction. Segments with NET <0 at 24 h, on the other hand, exhibited a reduction in aneurysmal bulging between 24 h and 1 wk from −41±10 to −23±11% (n = 12, P = 0.02).

Inotropic reserve was assessed with postextrasystolic potentiation (PESP) in 14 dogs, and with infusions of dopamine (11 dogs), and isoproterenol (13 dogs). PESP was the most potent intervention and produced a significant augmentation in NET in group 2 crystals at 1, 2, 4, 6, 8, and 24 h after coronary occlusion but only at 1 and 2 h in NET in group 3 crystals.

Thus, following experimental coronary occlusion, the evolution of ischemic segmental dysfunction is dynamic and variable. A significant degree of inotropic reserve, as assessed by PESP, dopamine, and isoproterenol, exists in segments with moderate ischemic dysfunction for 24 h but for only 2 h after coronary occlusion in those segments with the most severe ischemic dysfunction. In addition, at least some segmental sites with mild to moderate ischemic dysfunction at 24 h deteriorate further between 24 h and 1 wk after experimental coronary occlusion.

Received for publication 23 October 1978 and in revised form 14 June 1979.

INTRODUCTION

The extent of a myocardial infarction is an important predictor of subsequent morbidity, mortality, and residual left ventricular function in patients (1–4). Current evidence suggests that a zone of jeopardized myocardium coexists with a region of central infarction (5) and that infarct extension into the jeopardized zone may be relatively common in patients (4–7). Realistic expectations for the development of effective means of reducing the extent of ischemic ventricular dysfunction depend on the existence of zones of nonirreversibly injured myocardium with the potential for some degree of functional recovery and/or the reduction of aneurysmal systolic expansion of infarcted zones (8).

Histochemical (9), metabolic (10), electrocardiographic (11–14), rheological (15, 16), enzymatic (6), scintigraphic (17), and histologic (18) studies of jeopardized zones of myocardium have been carried out in experimental animals. However, the relationship between these parameters of ischemic injury and the segmental contractile properties of ventricular myocardium is unresolved.

The detrimental effects of ischemia on regional left ventricular contractile function have been appreciated by investigators for many years. However, important

 J. Clin. Invest. © The American Society for Clinical Investigation, Inc. · 0021-9738/79/10/1074/15 $1.00
Volume 64 October 1979 1074–1088

questions remain unanswered. Thus, the present study was undertaken in order to examine the segmental functional characteristics of ischemic myocardium and specifically to answer the following questions: (*a*) How does segmental function vary within and around ischemic areas of the left ventricle? (*b*) Do segments with differing degrees of ischemic dysfunction early after proximal occlusion of the left anterior descending coronary artery (LAD)[1] undergo subsequent changes in resting function over a 1-wk period? (*c*) After proximal LAD occlusion, what degree of contractile reserve persists in segments of myocardium with slight, moderate, or severe ischemic dysfunction? Further, what alterations in this contractile reserve occur during the 24 h after coronary occlusion?

To measure segmental ventricular function, we used ultrasonic pulse-transit piezoelectric crystals chronically implanted in the left ventricles of dogs (19, 20). Piezoelectric crystals used in this manner have been shown to be accurate, precise, relatively free of drift, easily calbrated, and to have a minimal effect on surrounding myocardium (20).

Assessment of latent segmental contractile reserve was achieved with three interventions. These interventions included postextrasystolic potentiation (21–23) and infusions of dopamine (24–27) and isoproterenol (28–32).

METHODS

Mongrel dogs weighing 25±3.3 kg (SD) were anesthetized with 30 mg/kg of pentobarbital intravenously, intubated, and placed on a Harvard respirator (Harvard Apparatus Co., Inc., Millis, Mass.). A thoracotomy was performed in the left 5th intercostal space under sterile conditions and the heart suspended in the pericardium. A Konigsberg (P22) catheter-tipped manometer (Konigsberg Instruments, Inc., Pasadena, Calif.) was placed into the left ventricular cavity through an apical stab wound. In other animals, a polyethylene catheter with a silastic valve was passed into the left ventricle. A Millar catheter (model PC-772, Millar Instruments, Inc. Houston, Tex.) could be inserted through the polyethylene conduit thus allowing the manometer to be zeroed to atmospheric pressure during the study. A catheter was inserted into the left atrium for pressure monitoring. The LAD was carefully dissected free of the epicardium, and a balloon occluder device placed around its proximal portion. In each of the animals studied, inflation of the balloon produced a temporary area of cyanotic myocardium over the anterior left ventricle. 5 MHz titanate-zirconate piezoelectric crystals 3–5 mm in diameter were then inserted through the myocardial wall and positioned near the endocardium. The endocardial crystal was paired with a second crystal sutured to the epicardium after its position had been adjusted to obtain an optimal signal by the method of Franklin et al. (19, 20). Ordinarily, five to six pairs of such crystals were inserted in or near the cyanotic region and one pair of crystals was inserted in the lateral portion of the left ventricle (Fig. 1). After pacing wires were attached to the right ventricle, the various catheters and wires were exteriorized between the scapulae and the incision was closed. Subsequently, the animals were studied at a time when they appeared to be fully recovered from the instrumentation surgery and free of infection. Internal jugular and carotid arterial catheters were placed 24 h before the beginning of the study under light anesthesia.

Left atrial and carotid artery pressures were measured with Statham P23 Db transducers (Statham Instruments Div. Gould, Inc., Oxnard Calif.). The maximum rate of rise of the left ventricular pressure (peak LV *dP/dt*) was recorded in millimeters of mercury per second from the micromanometer tipped catheters using an Electronics for Medicine RC differentiator (Electronics for Medicine, Inc., White Plains, N. Y.). Data from wall thickness crystals and LV pressures were recorded on a Hewlett-Packard 8-channel recorder (7758A) (Hewlett-Packard Co., Palo Alto, Calif.) interfaced with a Tektronix (465) oscilloscope (Tektronics, Inc., Beaverton, Oreg.).

Aortic systolic and diastolic, LV, and left atrial mean pressures were measured in milliliters of mercury. Segmental LV wall thickness was measured in millimeters assuming the speed of sound through myocardium to be 1.5 mm/μs (20). To correct for the variable initial separation of crystal pairs, measurements of wall thickness were expressed in terms of percent of control values. The data from the piezoelectric crystals were digitized by hand with a Graf/Pen (Science Accessories Corp., Southport, Conn.) and stored and processed by computer (DEC System-10, Digital Equipment Corp., Maynard, Mass.).

Three measurements were taken from the wall thickness data from which four parameters of wall motion were derived (Fig. 2). Diastolic wall thickness (point A, Fig. 2) was meas-

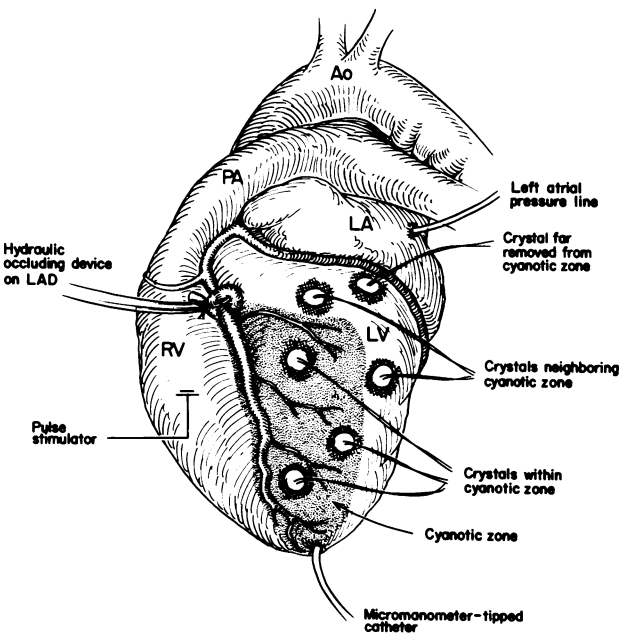

FIGURE 1 LAD occlusion is produced by inflation of a hydraulic occluding device encircling the LAD and producing an area of ischemia. Ultrasonic pulse-transit piezoelectric crystals are inserted to measure wall thickness within, near, and well removed from the cyanotic area.

[1] *Abbreviations used in this paper*: EDWTH, end-diastolic wall thickness; LAD, left anterior descending coronary artery; LV, left ventricular; NET, net systolic thickening; PESP, postextrasystolic potentiation.

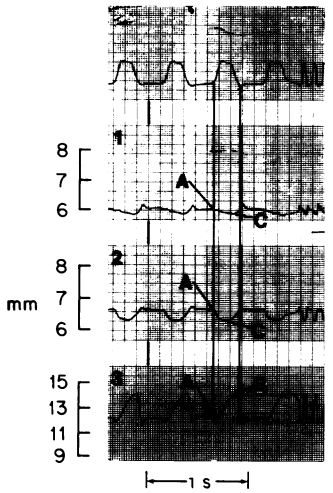

FIGURE 2 Wall thickness alterations during systole. A, end-diastolic wall thickness; B, systolic wall thickness; C, paradoxical systolic wall thinning. The first tracing is LV pressure. Of the three subsequent tracings representing wall thickness, the first two display paradoxical systolic wall thinning. The third tracing has a normal configuration.

ured just before the rapid upstroke of LV pressure. Systolic wall thickening (point B) was defined and measured as the maximal wall thickness attained between the initial rapid upstroke of LV pressure and peak negative LV *dP/dt*. The time period defined as "systole" extended from the initial rapid upslope of the LV pressure tracing to its return to its diastolic level; systole thus defined included both the isovolumic contraction and relaxation phases of ventricular systole. Paradoxical systolic thinning of the myocardial wall (point C) during systole was also measured. Early thinning of the myocardial wall may occur during isovolumic ventricular contraction (33, 34). Accordingly in such cases, wall thinning was not defined as paradoxical unless it persisted throughout at least 50% of the systolic period. The parameter, net systolic thickening (NET) (B-A or C-A, Fig. 2), was defined as the extent of systolic wall thickening minus the amount of paradoxical systolic thinning. Early diastolic thickening, which occurred during the period of isovolumic ventricular relaxation (an example of which is seen in Fig. 6B), was not included in the measurement of NET. Throughout the study, NET was expressed in terms of percent control NET; end-diastolic wall thickness was measured at the nadir of wall thinning occurring with atrial systole or just before the rapid upstroke of LV pressure if atrial systole could not be identified. End-diastolic wall thickness, like NET, was also expressed in terms of percent control to allow for variability in initial separation of crystals.

Dogs were studied from 7 to 14 d after their instrumentation at a time when they appeared to have fully recovered. All dogs were studied in an awake, unsedated state and were lightly restrained in a cradlelike device. In the first group of 20 dogs studied, base-line hemodynamic and wall thickness measurements were obtained. The balloon occluder was then inflated and measurements again taken 5 min after proximal LAD occlusion and every 30 min for the first 8 h and again at 24 h. 12 of these dogs survived at least 1 wk, at which time all measurements were repeated.

To assess residual contractile responsiveness after experimental occlusion, three groups of dogs received inotropic interventions. Each intervention was given at a preocclusion control time period and at 1, 2, 4, 6, 8, and 24 h post-LAD occlusion.

The first group (n = 14) of dogs received premature electrical stimuli from either a Medtronic 5325 programmable pacemaker (Medtronic, Inc., Minneapolis, Minn.) (stimulus duration 1.8 ms, 10–15 mA) or a Grass S88 stimulator (Grass Instrument Co., Quincy, Mass.) (stimulus duration 1 ms, 20–30 V). Pulses were delivered at the shortest R-stimulus interval at which ventricular capture and a compensatory pause occurred. The stimulus was delivered near the peak or on the downstroke of the T wave and resulted in maximal post-extrasystolic potentiation, consistent with the experience of others (21). 8–10 pulses were delivered at each time period with three to four intervening normal sinus beats, and the postextrasystolic responses measured and averaged.

In a second group of dogs (n = 11), dopamine was administered with a Harvard infusion pump (Harvard Apparatus Co.) at 5, 10, and 20 μg/kg per min for 5 min at each rate.

In a third group of dogs (n = 13), isoproterenol was infused for 2 min at 7, 14, and 27 μg/min. Infusions were intentionally limited to 2 min at each speed to avoid extreme elevations in heart rate and the secondary depression in myocardial performance known to occur in ischemic myocardium with longer infusion times (27–32).

At the conclusion of each study, the animal was sacrificed and the occluding balloon examined. In each case the balloon was noted to be fully and tightly inflated around the proximal LAD. The hearts were then placed in formalin. Fixation was initiated either shortly after sacrifice or within several hours of death in those dogs that died spontaneously. Transmural tissue blocks were obtained from each crystal site to include ≅0.5 cm of tissue on either side of an imaginary line connecting the epicardial and endocardial crystal pairs. The position of the inner crystal was usually found to be located within 1–2 mm of the endocardium. Histologic sections were cut and stained with hematoxylin and eosin. Photomicrographs of each histologic section were taken. The extent of histologic necrosis was then outlined and the total and necrotic areas planimetered. Extent of necrosis was then expressed as a percentage of total area and thus varied from 0 to 100. Histologic alterations were evaluated only in dogs not receiving an intervention and surviving between 24 h and 1 wk after LAD occlusion.

Segmental function was correlated with the extent of segmental histologic necrosis (see Fig. 8). In this analysis, samples of myocardium were examined from dogs sacrificed at 24 h, at 1 wk, or died spontaneously between 24 h and 1 wk in which autolysis did not interfere with the histologic assessment of necrosis. The study was initiated with 20 dogs, 13 of these survived to 24 h. One dog died shortly after 24 h postocclusion and supplied four segments of myocardium for segmental histologic-functional analysis. 12 dogs survived for 1 wk postocclusion, 4 of these were sacrificed and supplied seven segments for analysis; the remainder were allowed to survive beyond 1 wk. None of these seven segments demonstrated any significant interval functional change between 24 h and 1 wk postocclusion. The functional and histologic characterization of segments that did deteriorate significantly are discussed separately and illustrated in Fig. 3. Segments of dogs surviving longer than 1 wk were not used in the histologic-functional correlation. Functional data from this group of 20 dogs are used in the discussion of the functional alterations in dogs not receiving an intervention (Table I). 31 segments were added to the functional-histologic correlations from an additional series of dogs, instrumented, and studied in a manner identical to those dogs allowed to survive to 1 wk or beyond, but which were uniformly sacrificed at 24 h post-occlusion. Thus, a total of 42 segments is correlated with respect to function and histologic necrosis (see Fig. 8).

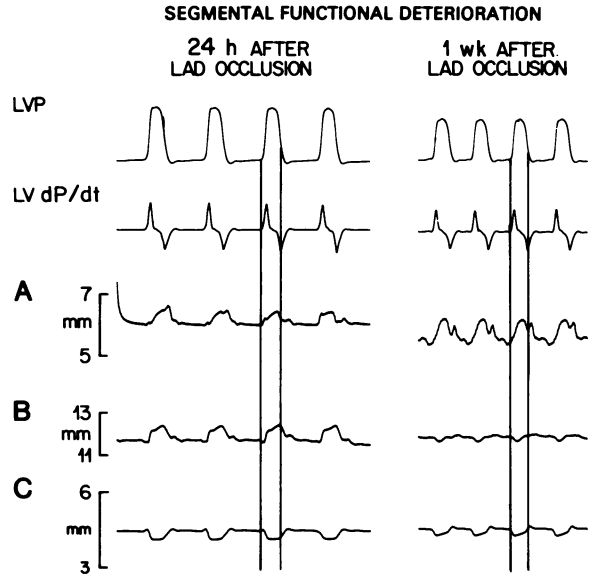

FIGURE 3 Wall thickness tracings from segments A, B, and C are displayed at 24 h (left panel) and 1 wk (right panel) after LAD occlusion. Note the marked functional deterioration that occurs in segment B, whereas that of segment A appears to improve slightly. The aneurysmal motion of segment C also decreases slightly during this time period. LVP, LV pressure; LV *dP/dt*, rate of LV pressure change.

For analysis of segmental function, crystal pairs were assigned to one of three groups. These groups were defined according to the value of the parameter NET, measured as percent control at 5 min after proximal LAD occlusion. The parameter NET was used for grouping the segments because it provided a measure of overall segmental function. Group 1 included segments with NET of ≥100–67%; group 2 included segments with NET of <67–0%; group 3 contained segments with NET values <0% of the control value for that segment. Thus, three groups were defined which ranged in severity of reduction with LAD occlusion from minimally reduced (group 1) to severely reduced with predominantly paradoxical wall motion (group 3).

For statistical comparisions between resting function and responses to an intervention a paired *t* test was used. For comparisons between resting hemodynamic and segmental function values at multiple time periods, an analysis of variance for repeated measures was used (35). When comparisons were between preocclusion control segmental function and later time periods, a one-sample *t* test was used with an alpha of 0.01 to allow for multiple comparisons. A Student-Newman-Keuls multiple comparisons procedure was used to test differences between groups of segments (36). A one-way analysis of variance was used to test for differences in responsiveness to an inotropic intervention between time periods (36). Dunnett's test (36) was used for multiple comparisons between control and other mean values. The null hypothesis was rejected when $P < 0.05$.

"Control" refers to the preocclusion control state; "resting" values were obtained after occlusion and before an intervention period. "Response" or "responsiveness" refers to the difference between a resting and postintervention state for each segment. Responsiveness is expressed as the difference between two percentages, thus in percentage points.

Some dogs died suddenly in the time period between 8 and 24 h postocclusion, or between 24 h and 1 wk postocclusion. The parenthetic values representing the reduced number of data points constituting each parameter are indicated in Table I.

RESULTS

Segmental function in dogs not receiving an intervention and followed for 1 wk (Table I). 20 dogs comprised this group. A resting tachycardia and mild diastolic hypertension were noted in the control state—probably as a result of the stress from an unfamiliar environment and the application of necessary light restraints. Immediately after proximal LAD occlusion, segmental LV function was altered to a variable degree. Group 1 segments ($n = 20$) were least altered functionally and retained between 67 and 100+% of control systolic thickening. Compared with control, NET was not altered for group 1 segments for any time period except 4 h postocclusion. Group 2 segments ($n = 22$) decreased to 36±4% (SEM) of

TABLE I
Dogs Not Receiving an Intervention and Followed for 1 wk after LAD Occlusion

	No.	Control	5 min	1 h	2 h	4 h	6 h	8 h	24 h		1 wk	
NET 1	20	100	92±5*	91±6*	88±5*	84±6*‡	86±8*	95±10*	87±11*	(14)	79±14*	(13)
NET 2	22	100	36±4*‡	29±8*‡	29±6*‡	19±7*‡	24±9*‡	23±11*‡	37±11*‡	(14)	30±12*‡	(14)
NET 3	31	100	−33±5*‡	−27±7*‡	−27±5*‡	−29±5*‡	−37±6*‡	−44±7*‡	−25±9*‡	(18)	−25±9*‡	(14)
AOS	19	147±4	140±5	136±4	134±5	133±5	130±4§	128±4§	124±3§	(12)	137±2§	(7)
AOD	19	105±3	105±3	104±3	101±3	100±3	101±3	97±3§	90±3§	(12)	96±4§	(7)
AOM	19	124±3	122±4	119±3	116±4	117±3	113±4§	114±3§	107±4§	(12)	117±3	(7)
ATM	18	11±1	17±2§	15±1§	15±2§	15±1§	16±2§	15±1§	14±2§	(10)	13±2	(4)
LV *dP/dt*	19	2164±131	1890±153§	1678±118§	1663±108§	1625±101§	1710±138§	1738±165§	1843±203§	(11)	1898±190§	(7)
HR	20	129±6	148±3§	149±3§	147±3§	149±3§	146±2§	150±4§	139±8	(13)	126±9	(12)

AOS, aortic systolic pressure; AOD, AOM, aortic diastolic and mean pressure; ATM, left atrial mean pressure; *dP/dt*, peak positive rate of LV pressure rise (mm Hg/s); NET 1, NET 2, NET 3 refer to net systolic wall thickening as percent control in groups 1–3. For definition of groups, see Methods. HR, beats per minute. All values are expressed as mean±SEM. All pressure measurements are in millimeters of mercury. No., number of crystals evaluated in each group at the initial control period. Values in parentheses indicate numbers constituting each parameter at 24 h and 1 wk.

* Significantly different from other two groups (Student-Newman-Keuls, $P < 0.05$).

‡ Resting value significantly less than preocclusion control $P < 0.01$ (one sample *t* test).

§ Significantly different from preocclusion control $P < 0.05$, (Dunnett's test).

control 5 min after LAD occlusion and remained significantly depressed at each time period through 1 wk postocclusion ($P < 0.001$). Group 3 ($n = 31$) segments were reduced to $-33\pm5\%$ 5 min after LAD occlusion ($P < 0.001$). The negative value of NET indicates that aneurysmal systolic wall thinning was present.

End-diastolic wall thickness (EDWTH) in the control period was 8.6 ± 0.26 mm. This figure is less than that of Sasayama et al. (37) who noted control EDWTH of 9.8 ± 0.4 mm. The difference in the two dimensions may be the result, in part, of the frequent placement of crystal pairs in our study near the apex where the LV wall is thinner. 5 min after LAD occlusion, EDWTH decreased significantly in groups 1, 2, and 3; this reduction was proportional to the corresponding degree of ischemic segmental dysfunction. Thus, at 5 min post-LAD occlusion, group 1 EDWTH (expressed as percent control) fell to $98.0\pm0.67\%$ ($P = 0.004$); group 2 fell to $94.7\pm1.44\%$ ($P = 0.001$), and group 3 fell to $91.6\pm0.97\%$ ($P < 0.001$). After occlusion, group 1 segments remained significantly depressed below control for 1 h, group 2 for 3 h, and group 3 for 6 h. Between 8 and 24 h EDWTH increased significantly in group 3 from 96.7 ± 1.68 to $105.6\pm4.43\%$ ($P = 0.0005$), whereas groups 1 and 2 did not demonstrate a further significant change.

No statistically significant further change in NET occurred in any of the three groups between 5 min and 24 h after occlusion. Each group was significantly different from the other two groups at each time period after coronary occlusion. However, in order to more closely examine segmental functional alterations between 24 h and 1 wk after occlusion, we recategorized the segments according to their functional status at 24 h. With this analysis, numbers of segments within each group were more uniform. Group A retained >50% of control NET ($n = 15$); those segments retaining between 0 and 50% were placed in group B, and those with <0% (paradoxical) in group C. Between 24 h and 1 wk postocclusion, group A segments did not change significantly; group B segments underwent a functional deterioration from 29 ± 6 to $8\pm11\%$ ($P = 0.04$, $n = 9$), whereas the paradoxical motion of group C decreased from -41 ± 10 to $-23\pm11\%$ ($P = 0.02$, $n = 12$). Because others (38), using similar techniques, had noted a significant improvement in function over this time period in segments with a moderate degree of ischemic dysfunction similar to our group B, we studied an additional 12 dogs with nine group B segments. In this later series, one of nine group B segments deteriorated compared to six of nine in our earlier series. Combining these results, it is evident that no significant overall change in function occurs in group B segments between 24 h and 1 wk ($P = 0.48$). Our later series did confirm, however, the significant reduction in paradoxical motion in group C as well as the lack of significant overall change in group A.

Despite the absence of a significant degree of overall change in groups A and B, some segments do undergo marked functional deterioration, an example of which is seen in Fig. 3. Examples of segmental deterioration were seen in both group A (in which 48% of segments decreased by at least 10 percentage points) and group B (45% deteriorated by 10 percentage points). In contrast only 7% of group C segments demonstrated this amount of deterioration.

During this time period, no significant change in EDWTH occurred in crystals in group A or B but those in group C increased significantly.

Our data thus suggest that segments with a mild to moderate degree of ischemic segmental dysfunction constitute a heterogeneous group: approximately half of the segments in either group A or B undergo some functional deterioration between 24 h and 1 wk after experimental cononary artery occlusion. Further work will be required to elucidate the pathophysiologic basis for the deterioration seen in some segments as well as for the improvement noted in others.

After LAD occlusion, significant but moderate increases in left atrial mean pressure and heart rate occurred and persisted through 8 and 24 h postocclusion, respectively (Table I). Significant decreases in LV *dP/dt* occurred with coronary occlusion and persisted for 1 wk postocclusion. Aortic systolic and diastolic pressures declined at 6 and 8 h postocclusion and remained depressed through 1 wk. The lowest individual systemic diastolic arterial pressure was 67 mm Hg, and the lowest mean systemic arterial pressure was 90 ± 3 mm Hg. Thus, coronary perfusion pressure was generally well maintained. No significant change in any of the hemodynamic variables occurred between 24 h and 1 wk postocclusion.

It is apparent from these data that the majority of ischemic impairment of segmental ventricular function occurs within 5 min after proximal LAD occlusion. However, further significant functional deterioration continues in at least some segments between 24 h and 1 wk postocclusion while others improve. Reduction in the aneurysmal bulging of segments in group C may result from decreased regional wall compliance with the occurrence of edema and inflammatory cellular infiltration (38, 39), a supposition supported by the finding of a concomitant increase in EDWTH during this time period.

Postextrasystolic potentiation (Figs. 4 and 5). 14 dogs received premature electrical stimuli. Large and significant increases in NET occurred with postextrasystolic potentiation (PESP) in segments in group 2 before occlusion and at each intervention period after coronary occlusion. The relative amount of PESP was greater in group 2 than in group 1 segments. Group 1

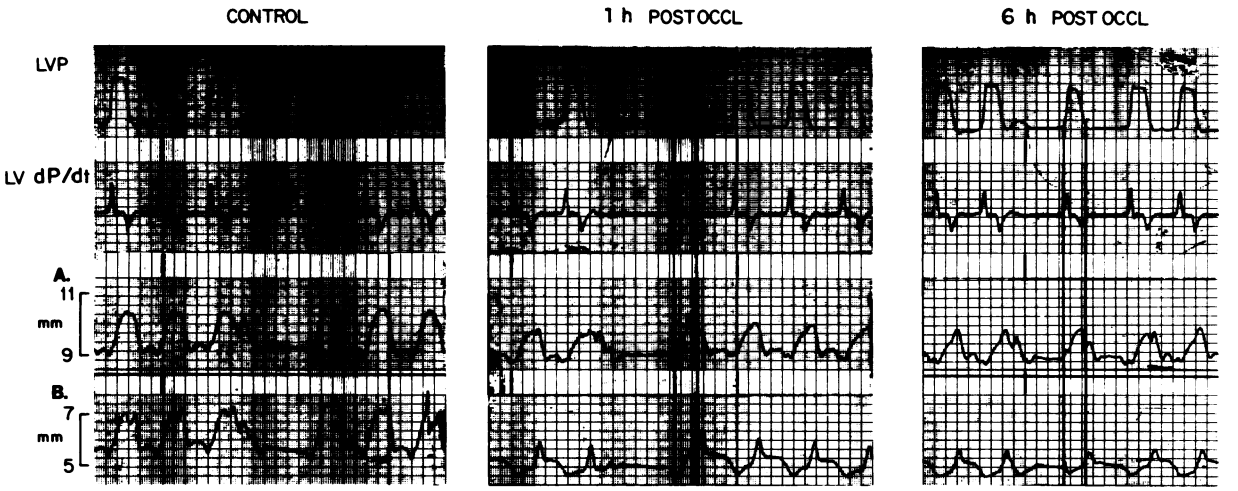

FIGURE 4 Postextrasystolic potentiation (PESP) in a preocclusion control time period (left panel) and at 1 and 6 h postocclusion (middle and right-hand panels). At 1 h postocclusion segment A is modestly reduced from control whereas segment B displays paradoxical systolic wall thinning. Following an extrasystole, augmentation occurs in both segments and is marked in segment B, in which paradoxical motion is reversed. Note the augmentation affects only a single beat. At 6 h postocclusion, the responsiveness to PESP is markedly reduced in both segments.

segments demonstrated a significant improvement in function through 8 h after coronary occlusion; at 24 h, only two crystal sites were available for analysis. Significant increases of a lesser magnitude occurred in segments in group 3, 1 and 2 h postocclusion but not thereafter. The amount of augmentation with PESP

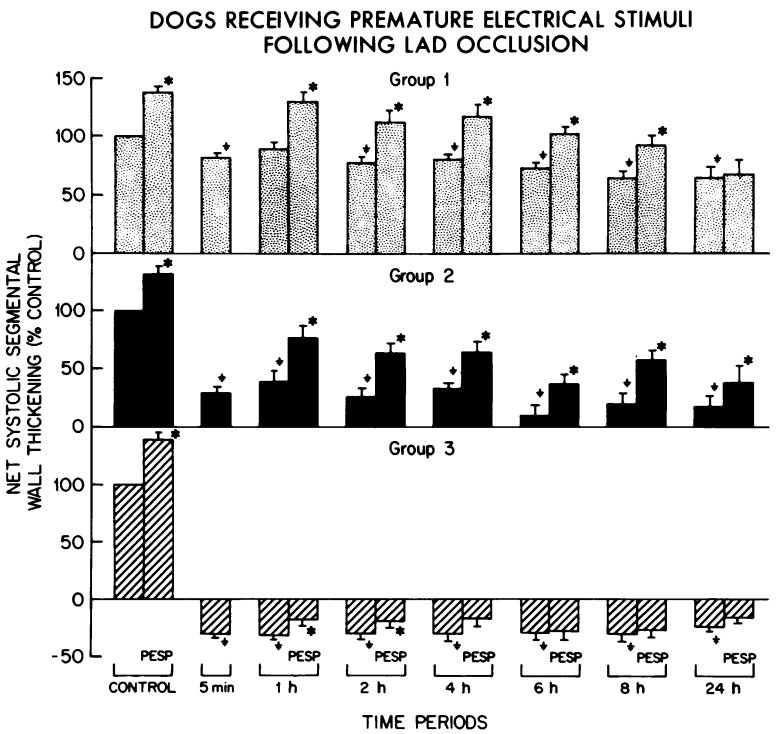

FIGURE 5 NET systolic wall thickening (as percent control) in a resting state and after PESP is depicted. Group 1 includes myocardial segments that retain ≥67% of control function 5 min after LAD occlusion; group 2 includes those with ≥0 and <67%; and group 3 < 0%. *, significant increase over resting value (paired t test), $P < 0.05$). ‡, significant decrease compared to preocclusion control (one sample t test $P < 0.01$).

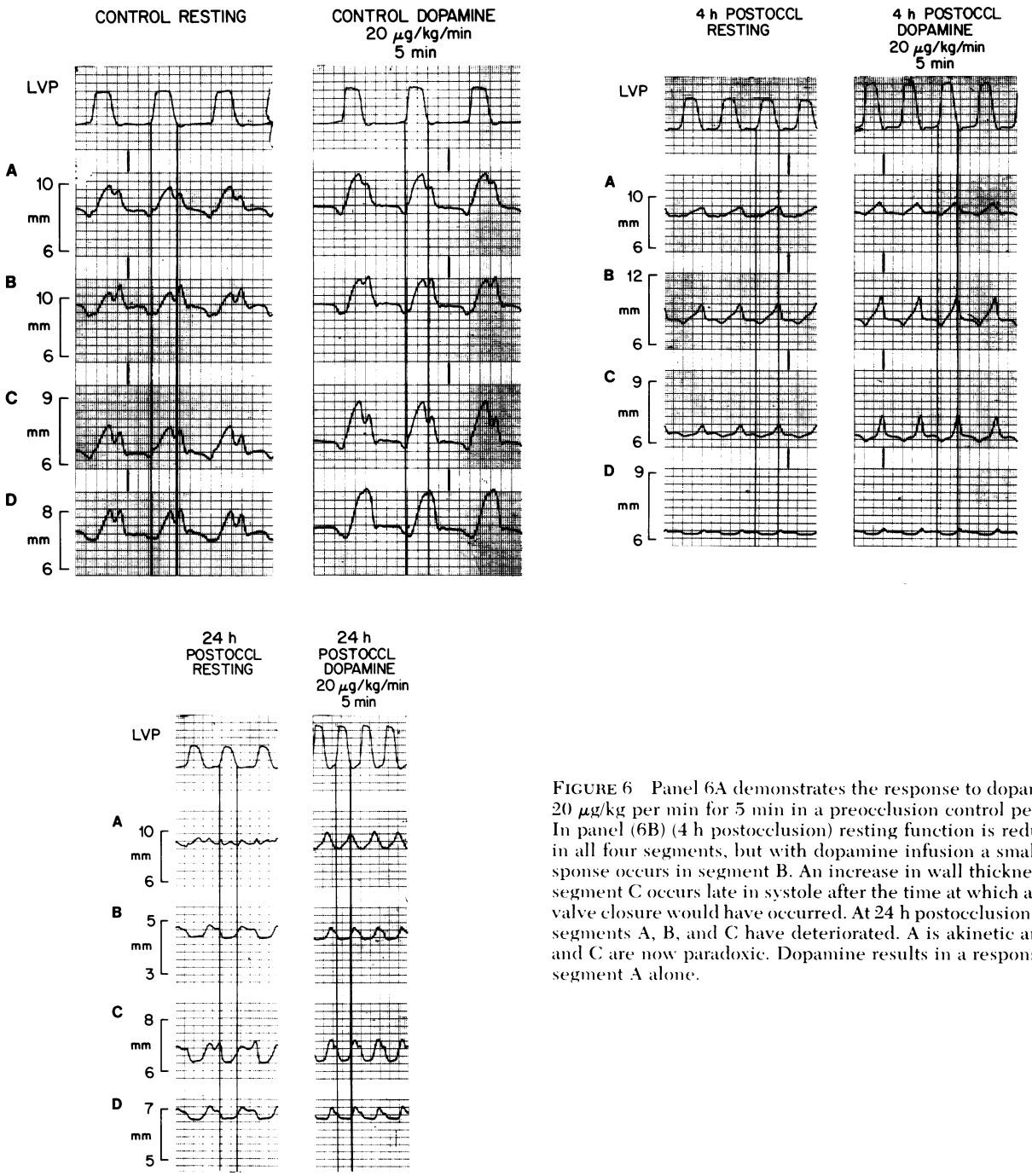

FIGURE 6 Panel 6A demonstrates the response to dopamine 20 μg/kg per min for 5 min in a preocclusion control period. In panel (6B) (4 h postocclusion) resting function is reduced in all four segments, but with dopamine infusion a small response occurs in segment B. An increase in wall thickness in segment C occurs late in systole after the time at which aortic valve closure would have occurred. At 24 h postocclusion (6C) segments A, B, and C have deteriorated. A is akinetic and B and C are now paradoxic. Dopamine results in a response in segment A alone.

after occlusion did not differ from that before occlusion for segments in either group 1 or 2. Segments in group 2 retained their responsiveness at least through 24 h postocclusion. At 1 h the mean difference between resting and augmented NET was 38±8 percentage points and at 8 h it remained essentially the same; however, by 24 h this responsiveness had deteriorated to 20±5 percentage points (Fig. 5).

Hemodynamic alterations that occurred with PESP consisted principally of decreases in aortic diastolic pressure and augmentation of LV *dP/dt* in the post-extrasystolic beat. Left atrial mean pressure after the electrical stimulus increased in the control period and at 2 h postocclusion but not at other time periods. These increases were associated with a significant decrease in LV segmental EDWTH. Others (40) have

noted a lack of consistent increase in LV end-diastolic pressure or volume after an extrasystole and have suggested that PESP is not dependent on increased preload following a compensatory pause (41, 42).

Dopamine infusion (Figs. 6A–C and 7A–C). Dopamine produced significant increases in NET LV segmental function at each infusion period in group 1 segments (n = 15). Over 24 h there was no significant decrease in the responsiveness of these segments to dopamine; resting function was significantly decreased at 24 h postocclusion (Fig. 7A). Segments comprising group 2 (n = 17) were reduced to 27±5% of control immediately after LAD occlusion. Infusion of dopamine produced a significant increase in net wall function at 1, 2, 4, and 8 h post-LAD occlusion but not at 24 h. In these segments there also appeared to be a shift in the dose response to dopamine to the right beginning ≅4 h after proximal LAD occlusion. Responsiveness of group 2 segments to dopamine at 20 μg/kg per min fell from 31 at 1 h to 21 percentage points at 8 h and to 18 percentage points at 24 h postocclusion, but these differences were not statistically different from one another (Fig. 7B).

Group 3 segments (Fig. 7C) displayed paradoxical systolic wall thinning through 24 h post-LAD occlusion. Resting NET systolic function of group 3 did not change during the 24 h. Dopamine produced a significant reduction in paradoxical motion only at 2 h postocclusion ($P < 0.04$) but at no other later infusion period. Because prominent increases in afterload occurred when dopamine was infused at 20 μg/kg per min, an index of segmental stroke work was calculated (where index of segmental stroke work = NET wall thickening × [aortic mean—left atrial mean pressure] as percent control). Statistical analysis of segmental function using this parameter gave identical qualitative results as using the parameter of NET wall motion alone for each of the three groups.

The principal hemodynamic alterations that occurred during dopamine infusions are summarized as follows. Aortic diastolic pressure fell at infusion rates of 5 and 10 μg/kg per min but aortic systolic, diastolic, and mean pressures rose at 20 μg/kg per min. Large and significant increases in peak positive LV dP/dt occurred at each infusion period. Heart rate showed a modest, but significant, increase with dopamine infusion at most time periods. Left atrial mean pressure tended to fall at infusion rates of 5 and 10 μg/kg per min of dopamine, but rose significantly at 20 μg/kg per min through 8 h postocclusion. Compared with preocclusion control values, significant decreases occurred in the resting-state aortic systolic pressures at 8 and 24 h postcoronary occlusion and in aortic mean pressure at 24 h. Significant increases in resting heart rate were noted at 6, 8, and 24 h postocclusion. No significant changes occurred in resting left atrial mean pressure; LV dP/dt was depressed below control levels at 8 and 24 h postocclusion.

Isoproterenol infusion. For group 1 segments resting function was depressed significantly below control levels between 1 to 3 h post-LAD occlusion. Significant increases in NET occurred at each infusion rate (7, 14, and 27 μg/min) at 1, 2, 4, and 6 h postocclusion, and at 7 and 27 μg/min at 8 h. No significant increases occurred at 24 h postocclusion. For group 2, resting function was significantly depressed below control levels at each time period after occlusion (NET = 33±4 at 5 min postocclusion). With isoproterenol infusions, significant increases in NET occurred at each infusion rate at 1, 2, 4, 6, and 8 h but no increase occurred at 24 h. Group 3 NET values were significantly less than control at each time period after LAD occlusion (NET = −36± at 5 min postocclusion). No significant changes occurred in NET with isoproterenol infusions at any time period after LAD occlusion.

Mean and diastolic aortic pressures fell significantly with isoproterenol at 1, 2, 4, 6, and 8 h but not 24 h postocclusion. Left atrial mean pressure rose significantly with occlusion and fell with isoproterenol infusions at 1, 2, 4, 6, and 8 but not 24 h post-LAD occlusion. Similarly, LV dP/dt and heart rate increased with isoproterenol infusion with each infusion rate at 1, 2, 4, 6, and 8 h but not 24 h. Because infusion volumes of isoproterenol were small, the lack of a significant response to the drug at 24 h probably reflects inadequate delivery to the animal rather than a large change in the dose-response curve.

In summary, dopamine and isoproterenol produced significant increases in segmental function for the initial 8 h after coronary occlusion in segments from group 2. The magnitude of responsiveness of segments comprising this group did not differ statistically post-LAD occlusion as compared to preocclusion. However, for group 2 segments there did appear to be a tendency toward decreasing responsiveness to dopamine and isoproterenol between 1 and 24 h after LAD occlusion. PESP produced a significant increase in group 2 segments throughout the 24 h period after LAD occlusion. In group 3 segments, improvement with PESP and dopamine was transient and appeared to be lost after 2 h postocclusion. Group 3 segments were unresponsive to isoproterenol at all times after LAD occlusion.

Histologic correlates (Fig. 8). In those dogs not receiving an intervention, LV segmental function, expressed as NET (percent control) at 24 h postocclusion was inversely related to the extent of segmental myocardial necrosis (r = 0.73, n = 42, $P < 0.00001$). The y-intercept for the least squares linear fit to the data is 49.7, suggesting that in this model NET function in the ischemic region at 24 h after coronary occlusion is reduced, on the average, by 50% in the absence of any necrosis. Fig. 8 illustrates this relationship. It is ap-

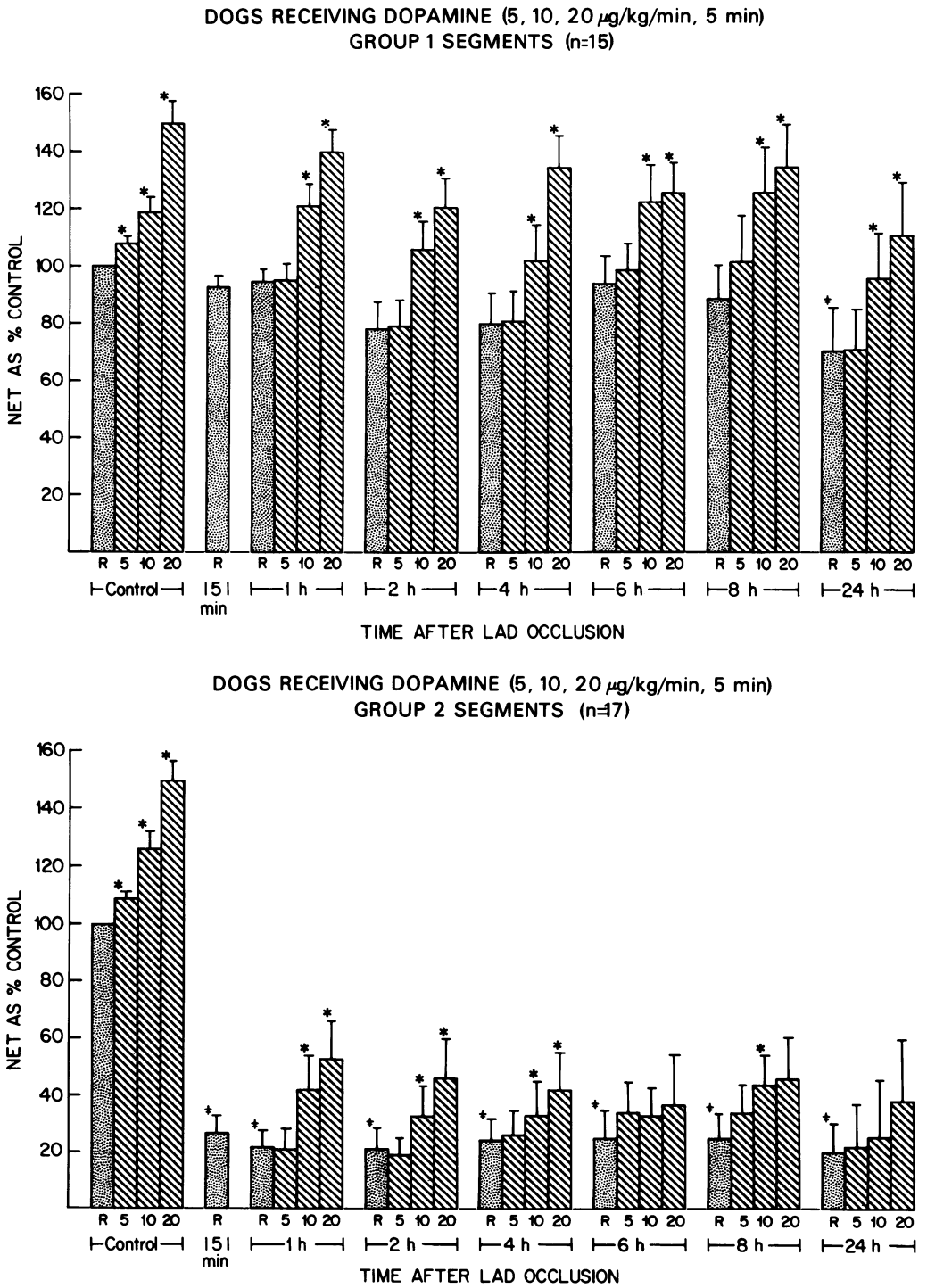

FIGURE 7A–C Responses of group 1 (7A), group 2 (7B), and group 3 (7C) segments to dopamine at 5, 10, and 20 μg/kg per min are demonstrated. Statistical symbols are defined in Fig. 5. R, resting state.

parent that there is considerable scatter in the data. Most segments showed a correspondence between the degree of functional impairment and the extent of segmental necrosis. Specifically, only two segments demonstrated NET systolic thickening ≥0 if the extent of histological necrosis for that segment exceeded 50%. In contrast, five segments were akinetic or paradoxical with <25% segmental necrosis. Thus, severe functional

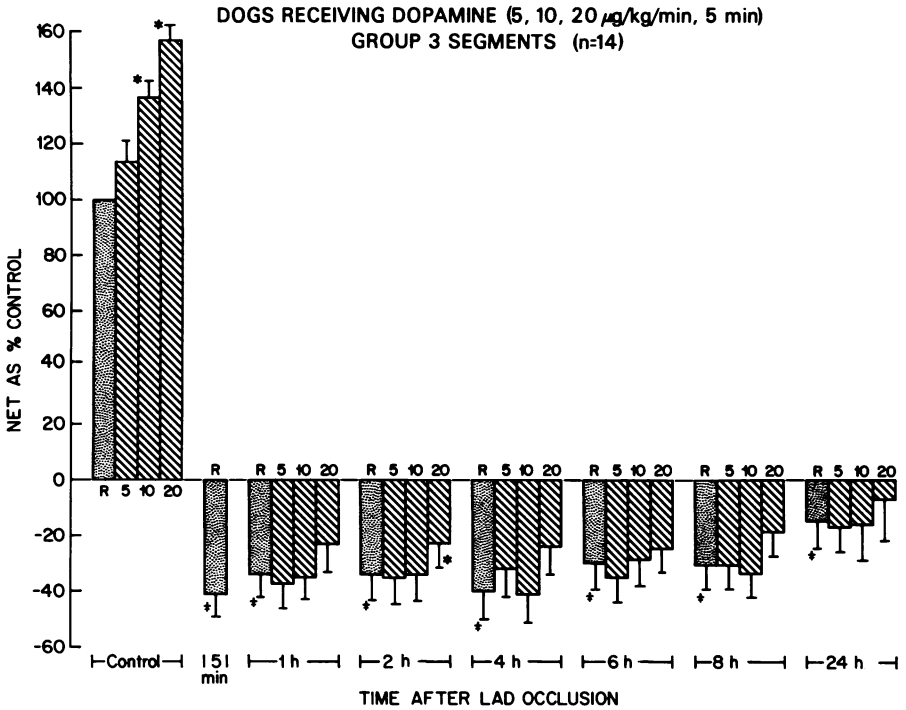

FIGURE 7 (*Continued*)

impairment may exist in the absence of advanced degrees of necrosis.

Histologic examination of group B segments revealed that those segments which improved between 24 h and 1 wk postocclusion were generally involved by patchy subendocardial necrosis involving <25% of total segment area, whereas those segments with late deterioration had more extensive necrosis with epicardial involvement.

DISCUSSION

Intensive efforts have been made over the last several years to develop pharmacologic (43, 44) or mechanical (45) interventions capable of protecting or "salvaging" ischemic myocardium. The relative size of such salvageable areas is controversial. Some recent evidence has suggested that a relatively large border zone exists between normal and necrotic myocardium (46–48). Other investigators have found that, after correcting for admixtures of normal and necrotic tissue, there is no region of size with an intermediate flow surrounding a grossly necrotic central zone (49). Relatively little is known, however, about the temporal evolution of segmental inotropic reserve after experimental myocardial infarction in the awake, unsedated dog. Therefore, in the present study, we have characterized the segmental LV functional properties of ischemic myocardium in both a resting state and after the serial administration of three inotropic interventions.

In this study, LV systolic wall thickness alterations after acute myocardial infarction were measured to quantitate segmental contractile function. The extent of systolic LV wall thickening is known to be a useful

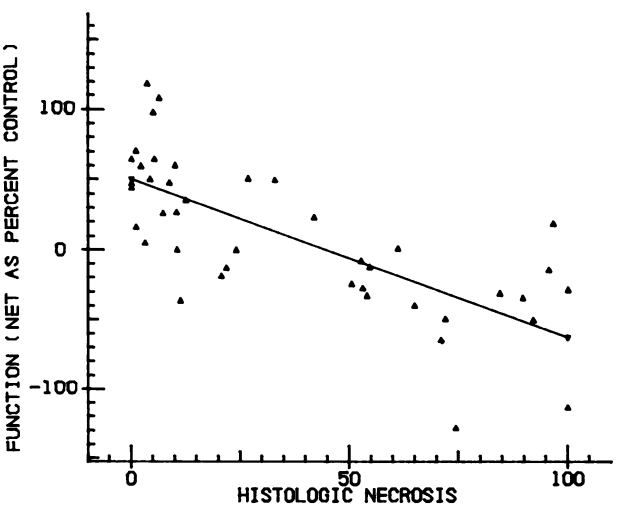

FIGURE 8 Segmental NET systolic wall thickening as percent control at 24 h postocclusion vs. the extent of histological segmental necrosis. Only dogs not receiving an intervention were included in the analysis. In 35 of the 42 segments histological data were obtained from dogs surviving 24 h postocclusion; the remaining 7 were obtained from animals sacrificed at 1-wk postocclusion. Note that marked functional depression may be present in the absence of a correspondingly severe degree of necrosis. The least squares linear regression equation is $y = -1.13x + 49.7$ (r, 0.73, $P < 10^{-4}$).

and accurate measure of regional LV function (37, 50, 51). Because myocardial ischemia tends to be most severe in subendocardial regions (52), the measurement of epicardial or endocardial segment length may over-or underestimate regional transmural wall function depending on the distance from the subendocardium that segment length is measured. Downey (53) noted an earlier loss of contractile force in deep layers of the myocardial wall with progressive reductions in LAD flow. The data of Stowe et al. (54) suggest that wall thickness measurements may be sensitive to ischemic dysfunction with moderate reductions in LAD flow as wall thickness was found to decrease proportionately more than mid-wall segment length or calculated segmental stroke work. Recently, Gallagher et al. (55) found an increased subendocardial functional loss compared with that in the subepicardium during graded coronary artery occlusion. On the other hand, Sasayama et al. (56) have noted qualitatively and quantitatively similar changes in ischemic segmental dysfunction by measuring segmental length vs. segmental wall thickness alterations during chronic ischemia in the conscious dog. Measurement of wall thickness quantitates transmural segmental contractile function more directly than epicardial strain gauges which may be relatively insensitive to subendocardial ischemia.

The physical characteristics of ventricular myocardium are complex and, in this model of experimental regional ischemia, heterogeneous. Thus, it is not possible to precisely quantitate the degree of influence that neighboring areas of myocardium may exert on the amount of systolic thickening or thinning recorded between individual pairs of crystals. However, piezoelectric crystals of the type used in this study are directional and imbedded in the LV wall where they are able to move freely without exerting tension on neighboring areas of myocardium. This method of measuring regional ventricular function can be expected to be more selective than length or strain gauges sutured to the epicardium. Lateral displacement of crystal pairs by shear forces might result in an overestimation of wall thickness; recent evidence suggests, however, that the magnitude of such shifts is minor (57). Epicardial electrocardiogram mapping techniques are sensitive to directional changes in epicardial ischemia, although they are relatively insensitive to subendocardial ischemia. Further, shifts in the magnitude of ST-segment elevations are influenced by a variety of factors other than ischemia (11, 12) and provide only an indirect measure of segmental function.

It is evident from an examination of Table I that the majority of segmental functional impairment that occurs with coronary occlusion in our model develops within 5 min. In addition, after LAD occlusion, no significant further change occurs in segmental function between 5 min and 24 h postocclusion. These results are consistent with those of other investigators using similar methodology (38). However, some segments of myocardium with mild (group A) to moderate (group B) degrees of ischemic dysfunction demonstrated further functional deterioration between 24 h and 1 wk postocclusion (Fig. 3). This deterioration occurred in the absence of a statistically significant overall functional change in group A or B. In contrast, those segments with predominantly paradoxical systolic wall thinning (group C) demonstrated an apparent improvement in function from $-41\pm10\%$ to $-23\pm11\%$ ($P = 0.02$) and a lesser incidence of deterioration. This apparent improvement probably represents decreased regional wall compliance with progressive stiffening of aneurysmal segments (39, 58) as a result of inflammatory cellular infiltration and edema; a partial recovery of contractile function is less likely (38). This conclusion is supported by the finding of a concomitant increase in EDWTH in these segments.

The hemodynamic alterations that occurred, *pari passu*, with proximal LAD occlusion and the production of segmental ventricular dysfunction consisted of elevations in left atrial mean pressure and heart rate with a reduction of LV dP/dt and, after 8 h of occlusion, of aortic systolic, diastolic, and mean pressures (Table I). At 1 wk postocclusion, however, heart rate and aortic mean pressure were no longer significantly depressed below control or left atrial mean pressure elevated. Further, no significant change in hemodynamic parameters occurred between 24 h and 1 wk postocclusion. Segmental function in some segments had deteriorated during this time period. Aortic diastolic pressure was depressed at 1 wk to 96 ± 4 mm Hg from a control of 105 ± 3; aortic systolic pressure declined from 147 ± 4 to 137 ± 2 at 1 wk. Such reductions, although statistically significant, would not be expected to produce any substantial reduction in coronary flow (59) or regional function (60). In addition, the absence of a significant overall functional deterioration in group A or B and an apparent improvement in function in group C segments between 24 h and 1 wk postocclusion argue against relative hypotension or tachycardia playing a major role in the observed deterioration of some group A or B segments. It should also be emphasized that functional alterations in group A and B segments between 24 h and 1 wk after proximal LAD occlusion are variable with some crystals deteriorating, whereas others improve or remain unchanged. Although such deterioration presumably occurs as a result of an extension or expansion of the ischemic process (6, 7, 61–63), additional work will be necessary to document precise mechanism(s) involved in the varied functional alterations occurring at these sites.

The findings of the present study differ from those of

earlier work (38) in several ways. In an earlier study, an improvement in the segmental function of marginally ischemic areas between 24 h and 1 wk after occlusion of the circumflex coronary artery was found (38). Our contrasting finding of a variable response with deterioration in at least some segments within such regions may be a result of differences in the manner in which groups of segments were defined or of a possible increased sensitivity of the measurement of wall thickness to ischemic functional alterations. Gross infarct size was not measured in either study, but the occurrence of a significant increase in left atrial mean pressure and a significant decrease in peak LV *dP/dt* after coronary occlusion suggest more severe LV dysfunction in the present study in comparison to earlier work (38) in which these changes were not seen. Heart rate at 1 wk was also higher (126±9) in our study than in the earlier study (107±8) suggesting a greater degree of LV dysfunction, although other factors such as differences in the distribution of ventricular receptors with vagal afferents (64) may also have played a role. In addition, as detailed below, the present study has characterized the degree of contractile reserve remaining in segmental areas of myocardium with varying degrees of resting functional impairment.

Approximately 80% of myocardial oxygen consumption is used for contractile processes (65); hence, ischemic areas may exist which, although not actively contracting, are nonetheless still viable and capable of returning to nearly normal functional levels. To determine the functional reserve of such areas, three types of inotropic interventions were used including PESP and infusions of dopamine and isoproterenol.

PESP may be a result of an augmentation in slow-channel calcium entry (66), an increase in calcium release from the sarcoplasmic reticulum (67, 68) or a compensatory pause following the premature stimulus (41). PESP has been demonstrated in both normal and ischemic myocardium (69) and provokes a nearly maximal contractile response in isolated, isometrically contracting papillary muscles (70). In the present study, segments with resting function reduced to between 0 and 67% of control (mean 29±6% at 5 min postocclusion) were able, with PESP, to double the extent of systolic wall thickening at 1, 2, 4, 6, 8, and 24 h postocclusion (Figs. 4 and 5). The absolute magnitude of the postextrasystolic response was similar to that of the relatively nonischemic group 1 segments. Responses seen after coronary occlusion did not differ significantly from pre-occlusion values for either group 1 or 2 segments. These results are comparable to observations made in patients with ischemic heart disease during ventriculography (40). In segments of myocardium with paradoxical systolic thinning of the LV wall, PESP produced a significant improvement in function at 1 and 2 h but not at 4, 6, 8, or 24 h postocclusion. Sueur and Urschel (23) showed in isolated perfused isovolumic canine hearts that continuous paired pacing under ischemic conditions resulted in a rapid decrease in responsiveness after 1 min of stimulation. Cessation of stimulation was associated with a further depression of ventricular function. In the present study, not only was PESP delivered intermittently with a minimum of 1 h between intervention periods, but pacing was not continuous, given rather no more often than every fourth beat. Therefore, it is unlikely that the loss of response after 2 h in the segments with severe functional depression resulted from a marked increase in myocardial oxygen consumption produced by PESP itself.

Crozatier et al. (71) quantified PESP for 2 h postocclusion in ischemic segments of myocardium with techniques similar to those of the present study. These authors noted a large amount of PESP in marginal segments through 2 h but a loss of PESP in areas with paradoxical motion after only 3 min, whereas in our study responses were seen for 2 h postocclusion (Figs. 4 and 5). In this latter study (71), however, premature stimuli were not coupled in a constant manner to the preceding sinus beat. Because the amount of PESP varies directly with the prematurity of the stimulus (21), it is possible that some degree of PESP may have been missed in the latter study (71).

Dopamine enhances myocardial contractility and increases stroke volume and cardiac output. It produces mesenteric and renal vasodilation by action on a dopamine receptor, but at larger doses a pressor response occurs (25). Dopamine enhanced LV segmental contractile function as measured by an increase in NET in LV segments reduced to 0–67% of control at 1, 2 and 4 h postocclusion but not consistently at 6, 8, or 24 h despite large increases in LV *dP/dt* (Figs. 6A–C and 7A–C). Those segments with paradoxical motion showed a significant improvement with dopamine infusion only at 2 h postocclusion. Those segments retaining >67% of control net function (group 1) improved significantly during all infusion periods but did fail to respond to 5 μg/kg per min after occlusion (Fig. 7A).

Isoproterenol is known to produce an improvement in the contractile state of the heart (28–30) but at the expense of increased lactate production (72) and epicardial ST elevation (27, 44). Isoproterenol significantly enhanced the function of segments reduced to 0–67% of control at 1, 2, 4, 6, and 8, but not at 24 h postocclusion. Isoproterenol did not significantly modify the function of those segments with paradoxical systolic wall thinning at any time after LAD occlusion. It produced marked increases in heart rate and LV *dP/dt* but lowered aortic diastolic pressure. Others (27) have noted a detrimental effect of isoproterenol on regional function of ischemic myocardium not

shared by dopamine. Increased ST-segment elevation (27) and relative subendocardial ischemia (73) occur with isoproterenol in contrast to dopamine infusions.

It is apparent from the results presented here that a significant amount of contractile reserve exists, following LAD occlusion, in areas of myocardium when resting function has been reduced to 0 and 67% of preischemic values. This contractile reserve persists through at least 24 h in such areas. Areas with more severe functional impairment, characterized by paradoxical motion during systole, retain the ability to respond to inotropic interventions for only 2 h postocclusion. After this time most segments lose their ability to respond to inotropic stimuli but do not change their resting function. PESP, by augmenting the contractility of a single beat, appears to be an effective and powerful inotropic intervention to detect residual contractile function in ischemic myocardium. Pharmacologic interventions such as isoproterenol and, to a lesser degree, dopamine alter the oxygen supply-demand ratio in ischemic zones (74) with the resultant development of regional acidosis (75) or a combination of ATP depletion and inorganic phosphate accumulation (76). Lack of response to these pharmacologic agents should not therefore, be construed to necessarily imply the absence of functionally responsive or viable myocardium.

The histologic results obtained in the present study demonstrate that some caution must be taken if inferences regarding segmental ventricular function are drawn from the degree of histologic necrosis present in such areas. Our results demonstrate that severe functional impairment may exist in the presence of a comparatively mild degree of necrosis. Such findings are consonant with other studies in humans (77, 78) and emphasize the need for both a functional and morphologic evaluations of interventions designed to protect ischemic myocardium.

The data obtained in the present study lend support to the concept that there are areas of functionally depressed myocardium with at least the potential for a return to a more nearly normal contractile state if an appropriately timed protective intervention were administered. Although the findings of the present study confirm the presence of functional "border" or "jeopardized" regions for 24 h to 1 wk after experimental coronary occlusion, the data do not allow one to determine the size of such zones or the pathophysiologic basis for the observed functional abnormalities. Functional deficits observed in border zones may be a result of an intermediate reduction in coronary perfusion with a resultant decrement in performance (79, 80) or the result of a loss in numbers of contractile units with the functioning myocytes retaining normal levels of coronary perfusion, thus implying a sharply defined border zone between normal and necrotic tissue (15, 49). Further studies are necessary to clarify these issues and to quantify the relative size of such functionally depressed areas following coronary occlusion.

In summary, the present study has (*a*) delineated the variable segmental functional responses that occur in ischemic myocardium after proximal LAD occlusion over a 1-wk period in the awake, unsedated dog; (*b*) identified segments of myocardium that undergo progressive functional deterioration between 24 h and 1 wk postocclusion; (*c*) quantitated the temporal alterations in inotropic reserve of segments of myocardium with varying degrees of functional impairment over a 24-h period; and (*d*) characterized a general relationship between segmental histologic alterations and the corresponding degree of functional impairment while emphasizing that severe functional depression may exist in the absence of extensive necrosis. Future characterization of the ability of various interventions of "protect" ischemic myocardium should ideally also include an assessment of the preservation of regional ventricular function.

ACKNOWLEDGMENTS

The expert technical assistance of Ms. Judy Ober, Ms. Janice McNatt, Mrs. Marilyn Kee, Mr. David Perry and Mr. Gifford Ramsey is gratefully acknowledged. The statistical assistance of Dr. Richard Browne and the computer programming by Vic Summerour are also appreciated. The secretarial assistance of Mrs. Belinda Lambert, Ms. Laurie Grey and Mrs. Mary Thomas is also appreciated.

The work was supported in part by National Institutes of Health Ischemic Specialized Center of Research grant HL-17669 and the Harry S. Moss Heart Fund.

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