Early Recovery of Regional Performance in Salvaged Ischemic Myocardium following Coronary Artery Occlusion in the Dog

JOHN R. DARSEE, ROBERT A. KLONER, and EUGENE BRAUNWALD, *Cardiovascular Division of the Department of Medicine, Harvard Medical School, Peter Bent Brigham Hospital, Boston, Masssachusetts 02115*

ABSTRACT Although numerous agents have been shown experimentally to protect ischemic myocardium, a critical unanswered question is whether function is preserved in the salvaged tissue. Accordingly, 38 open-chest dogs had measurements of percent segment length shortening (%SS) and velocity of segment length shortening either in midmyocardial or subepicardial and subendocardial ischemic segments before and after 60 min of left anterior descending coronary artery occlusion during 5 h of reperfusion; 10 additional dogs were subjected to 3 h of coronary occlusion followed by 72 h of reperfusion. 15 min after coronary artery occlusion, radiolabeled microspheres were injected into the left atrium for measurement of regional myocardial blood flow, and dogs were treated with 1 mg/kg i.v. (n = 23) of an anti-inflammatory drug, flurbiprofen or an equal volume of saline (n = 25). The ischemic myocardium-at-risk for necrosis was determined by injecting methylene blue dye into the left atrium with the coronary artery reoccluded at the end of the reperfusion period, slicing the left ventricle into thin transverse sections, and measuring the areas of each slice that were not perfused (pink unstained tissue) by methylene blue. The quantity of necrotic tissue in each transverse section was measured by planimetry after incubation of the slices in triphenyltetrazolium chloride, and by direct histological examination in dogs with 72 h of reperfusion.

Regional myocardial blood flow of the ischemic segments between the ultrasonic dimension crystals was similar in treated (0.34±0.03 ml/min per g) and control dogs (0.35±0.03 ml/min per g). In saline-treated control dogs subjected to a 1-h coronary occlusion, 17.9±1.8% of the myocardium-at-risk became necrotic, but in flurbiprofen-treated dogs none of the tissue became necrotic. In saline-treated dogs passive lengthening of the previously ischemic segments persisted through 5 h of reperfusion in all three regions of myocardium after a 1-h coronary occlusion. In flurbiprofen-treated dogs regional function returned to normal within 5 min of reperfusion in both the subendocardium (%SS preocclusion = 17.2±2.0%; 5 min reperfusion = 17.8±3.1%; P = NS) and in the midmyocardium (%SS preocclusion = 17.8±2.2%; 5 min reperfusion = 17.9±2.3%; P = NS) and was not significantly different after 5 h of reperfusion from what it was before coronary occlusion. In the subepicardium of treated dogs regional function began to improve within 15 min of drug administration even during coronary occlusion. Regional function was not different from preocclusion values after either 5 min or 5 h of reperfusion (%SS preocclusion = 21.0±2.4%; 5 min reperfusion = 20.6 ±3.8%; P = NS). In dogs subjected to 3 h of coronary occlusion and 72 h of reperfusion, the administration of flurbiprofen was also associated with significantly smaller infarcts and a significantly more rapid rate of functional recovery than in control dogs.

Thus, it appears that flurbiprofen not only decreased the quantity of necrosis in tissue made ischemic after coronary occlusion and then reperfused, but also allowed more rapid recovery of segmental function in ischemic but nonnecrotic tissue and in tissue with patchy necrosis; such recovery did not occur in equally ischemic myocardium in untreated control dogs. Earlier functional recovery of reversibly injured tissue following prolonged periods of ischemia is an additional important role for agents that protect ischemic myocardium from necrosis.

INTRODUCTION

Previous investigations have shown that numerous interventions can potentially prevent or reduce the

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number and severity of dangerous arrhythmias originating in ischemic myocardium (1, 2), and that other agents limit the extent of necrosis following experimental coronary occlusion (3, 4). Although it seems inherently beneficial to salvage some of the ischemic myocardium-at-risk from proceeding to the stage of necrosis, thereby decreasing the percentage of left ventricular tissue involved in the infarct, it is unknown whether the salvaged tissue functions normally and contributes to the overall performance of the left ventricle. It is possible that although the salvaged tissue does not become necrotic by histologic criteria, its function may remain impaired and it either may act as a stiff, noncontracting segment or may continue to undergo passive lengthening, in either case impairing overall ventricular function.

The time-course of functional recovery of myocardial tissue following coronary occlusion has been studied in the conscious dog (5–7) and in patients with clinically documented myocardial infarction in the absence of any intervention (8, 9). These investigations have shown that the rate of recovery of the marginal ischemic tissue is extremely slow. It would be important to determine whether ischemic tissue salvaged by an intervention recovers contractile function, and if so, how rapidly. If the salvaged ischemic tissue is capable of contributing to overall ventricular performance, myocardial protection would have even greater importance than heretofore considered. The present study was undertaken to determine whether flurbiprofen, an agent shown previously to be capable of salvaging myocardium-at-risk of developing necrosis as a consequence of a sustained coronary occlusion (10), also preserves the functional characteristics of the salvaged tissue.

METHODS

Animal preparation and instrumentation. 56 mongrel dogs of either sex weighing 24–31 kg were anesthesized with thiamylal sodium (30 mg/kg i.v.), intubated, and mechanically ventilated. Basal body temperature was maintained within ±0.5°C by an external heat source. A thoracotomy was performed (under sterile conditions in 12 of the dogs) through the left fifth intercostal space; the lungs were retracted and a pericardial cradle was created to support the heart. Catheters were placed into the left atrium for injections of microspheres and dyes, into the left carotid artery for monitoring arterial pressure and for withdrawal of a reference blood sample during the injection of microspheres, and into the left jugular vein for intravenous injections. Either a micromanometer-tipped pressure catheter (Millar Instruments, Houston, Tex.) or a miniature implantable pressure gauge (Konigsberg Instruments, Pasadena, Calif.) was placed into the left ventricle through a stab wound in the apex. A 14–16-mm segment of the left anterior descending (LAD)[1] coronary artery was dissected free from adjacent tissues above the first diagonal branch, care being taken to isolate a segment of the artery without branches. A circumferential electromagnetic cuff flowprobe (Biotronix Laboratories, Inc., Silver Spring, Md.) was placed around the proximal part of the isolated segment of the LAD coronary artery and energized with a Biotronix (model BL 620) electromagnetic flowmeter. The distal part of the isolated coronary segment was left free for later placement of a vascular clamp.

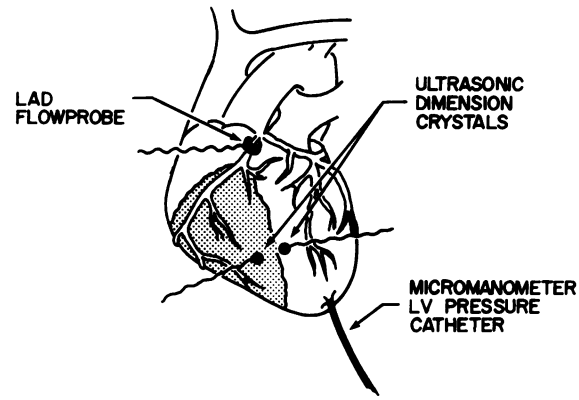

FIGURE 1 Diagram of the experimental preparation showing the positions of the coronary flowprobe, left ventricular (LV) pressure transducer, and relative positions of the ultrasonic dimension crystals.

Ultrasonic crystals were placed in the myocardium for measuring instantaneous myocardial segment length according to the following method. First, the LAD coronary artery was briefly occluded in order to determine the epicardial region of reduced blood flow. This was accomplished by injecting a 4% solution of sodium fluorescein (0.5 ml/kg) into the left atrium; this results in a nonfluorescent region of epicardium perfused by the occluded coronary artery when an ultraviolet light (340 nm) is used to illuminate the heart. We have previously shown that the tissue that is not perfused by fluorescein using this technique has values for regional myocardial blood flow (RMBF) of <0.4 ml/min per g (10). The border between fluorescent and nonfluorescent epicardium was outlined by painting a thin line of gentian violet over the line of demarcation, before the fluorescein was completely washed out of the myocardial capillaries. A pair of ultrasonic dimension crystals was implanted in the region of the left ventricular equator at the midmyocardial level in 34 dogs and one pair in the subendocardium and one in the subepicardium in the remaining 22 dogs. The midmyocardial depth was chosen for most of the experiments since we wished to analyze the function of tissue that remains ischemic for a prolonged period but does not become infarcted. Previous experiments in our laboratory have shown that infarction does not usually extend outward as far as the midmyocardium after a 1-h coronary occlusion followed by reperfusion (11). One of the crystals was positioned at the ischemic border as outlined above and the other ~10 mm within the ischemic zone on an approximate equatorial relationship with the first crystal (Fig. 1). The position of the crystals was confirmed at necropsy. This particular region of the ischemic zone was analyzed because it represents the

[1] *Abbreviations used in this paper: dSL/dt*, rate of change of segment length; *dP/dt*, rate of change of pressure in the left ventricle; DP_{40}, developed pressure of 40 mm; EDL, end-diastolic length; LAD, left anterior descending; LVEDP, left ventricular end-diastolic pressure; %SS, percent segment length shortening; RMBF, regional myocardial blood flow; TTC, triphenyltetrazolium chloride.

ischemic tissue at risk for necrosis with the greatest potential for salvage by a variety of agents, primarily because it has the highest level of RMBF within the ischemic zone (10).

The ultrasonic crystals were piezoelectric transducers, 2 mm Diam and resonant in the 800 kHz radial mode. An ultrasonic transit-time dimension gauge produced a burst of ultrasound energy in the frequency range of ~800 kHz which was propagated from the transmitting transducer to the receiving transducer. The instrument provided a direct measurement of the transit time of each ultrasound burst, and generated a proportional analog voltage (12). The instantaneous distance between the transducers (and therefore the length of the subtended myocardial segment) was calculated from the analog signals according to the following equation: $d = c \cdot T$, where d = distance (cm), c = speed of sound in myocardial tissue (1.58×10^5 cm/s), and T = transit time (s). Zero suppression allowed for the display of small dimensional changes on an expanded scale without affecting the accuracy of calibration. Calibration was accomplished by substituting pulses of precisely known duration in 1-μs increments from a crystal-controlled pulse generator with a stability of ±0.1%.

Experimental measurements. Before, during, and after occlusion of the LAD coronary artery, several variables were measured. The left ventricular micromanometer-tipped pressure transducer was calibrated in vivo using pulsatile aortic pressure and mean left atrial pressure signals recorded simultaneously through fluid-filled catheters. Left ventricular pressure was recorded and electronically amplified to measure left ventricular end-diastolic pressure (LVEDP). The rate of change of pressure in the left ventricle (*dP/dt*) was obtained electronically from the left ventricular pressure signal using an operational amplifier connected as a differentiator. A triangular wave signal with known rate of change (slope) was substituted for pressure to calibrate *dP/dt*. Mean and pulsatile flow in the LAD coronary artery were measured throughout the experiment with the cuff flowprobe. Zero flow was determined after the initial coronary occlusion and twice briefly (<5 s) during the reperfusion period for the purpose of minimizing the influence of electronic drift on the calibration. The flowmeter was calibrated *in situ* by inducing cardiac standstill at the end of the experiment and perfusing the LAD coronary artery with heparinized blood from an infusion pump with a variety of known flow rates. From the signal produced by the transit-time dimension gauge, the end-diastolic length (EDL) and end-systolic length (ESL) of the subtended myocardial segment were determined and the percent segment shortening (%SS) was calculated from the formula: %SS = (EDL − ESL)/EDL × 100%. The segment length signal was electronically differentiated to obtain the velocity of segment length shortening, that is, the rate of change of segment length (*dSL/dt*). The rate of change of segment length (velocity of shortening) was only applicable to segments of myocardium undergoing net shortening during systole; thus, *dSL/dt* was ignored in any myocardial segment with net systolic lengthening. The *dSL/dt* channel was calibrated using a triangular wave signal substituted for segment length in a similar fashion as described for calibration of *dP/dt*.

Experimental protocol. 44 of the dogs were designated for 1 h of coronary occlusion followed by 5 h of reperfusion. To assess the recovery of regional function under conditions in which the myocardium remained ischemic for a considerably longer period of time and thereby provide a more rigorous comparison of control and treated groups, 12 dogs operated under sterile conditions were subjected to 3 h of coronary occlusion; regional and global function were assessed during a subsequent 72-h period of reperfusion to allow for a greater degree of recovery and to be able to assess infarct size by means of standard histologic criteria and to compare the results with those obtained using triphenyltetrazolium chloride staining. Just before LAD coronary artery occlusion, the dogs were randomized to either the treated or control group on the basis of a random odd or even number generated by a computer program. Base-line values for all measured hemodynamic variables were recorded at paper speeds of 25 and 100 mm/s (Gould Inc., Cleveland, Oh.) and used for future comparisons. Between measurements all signals were recorded continuously at a paper speed of 0.25 mm/s. To be able to account for possible microsphere "washout" in infarcted tissue, $\sim 2.0 \times 10^6$ radioactive microspheres (8–10 μm Diam) labeled with ^{46}Sc were injected into the left atrium just before coronary occlusion in the 12 dogs to be subjected to 3 h of coronary occlusion followed by 72 h of reperfusion. The LAD coronary artery was clamped with a vascular clip distal to the coronary flowprobe. Any dog having one or more episodes of ventricular fibrillation (always within the first 15 min after coronary occlusion) was excluded from further study. 15 min after LAD coronary occlusion, RMBF was determined by injecting $\sim 2.0 \times 10^6$ radioactive microspheres (8–10 μm Diam) labeled with ^{141}Ce into the left atrium. Dogs randomized to the treated group received 1 mg/kg flurbiprofen intravenously and control dogs received 1 ml/kg saline.

Flurbiprofen is a potent anti-inflammatory agent that inhibits the enzyme cyclooxygenase, and thus the subsequent production of endoperoxides and prostaglandins PGE_2 and $PGF_{2\alpha}$, which participate in the inflammatory process. It also appears to interfere with the kinin and histamine systems, stabilize lysosomal membranes, suppress leukocyte motility and phagocytosis, and interfere with platelet aggregation (10).

50 min after coronary occlusion in the dogs subjected to a 1-h coronary occlusion, lidocaine (1.5 mg/kg) was administered intravenously to suppress the development of reperfusion arrhythmias. 60 min after coronary occlusion in this subgroup of dogs, the clamp was removed and reperfusion was allowed to occur. We used a model in which reperfusion was allowed after 60 min in some of the dogs because of its clinical relevance to patients who are candidates for acute myocardial revascularization or intracoronary fibrinolysin administration (13), and because we wished to analyze the function of tissue in which no necrosis had occurred.

In the remaining dogs operated under sterile conditions, the coronary clamp was removed after 3 h of coronary occlusion; the leads from the ultrasonic crystals, the pressure gauge, and the coronary flowprobe were tunneled subcutaneously and exteriorized between the scapulae; and the thoracotomy was closed in layers.

Any dog having one or more episodes of ventricular tachycardia lasting > 5 s or ventricular fibrillation during reperfusion was also excluded from the study. Recordings of hemodynamic variables at paper speeds of 25 and 100 mm/s were made every minute during the first 10 min of reperfusion, every 5 min for the next 50 min, and then hourly for 5 h. In the dogs subjected to 3 h of coronary occlusion, hemodynamic variables were also recorded every 12 h for 72 h. Either 6 or 75 h after coronary occlusion the dogs received a second injection into the left atrium of microspheres labeled with ^{113}Sn with the LAD coronary artery patent. This was done to determine whether RMBF during reperfusion was similar in the myocardial tissue between the ultrasonic crystals in treated and control dogs, and whether flurbiprofen had an influence on RMBF in the entire ischemic bed during reflow. Following microsphere injection, all dogs received a 30-s infusion of methylene blue (not pH-dependent), 3 ml/kg into the left atrium with the LAD coronary artery reoccluded

to provide a visual demarcation between the nonperfused myocardial tissue distal to the coronary clamp and the perfused tissue supplied by unoccluded vascular beds. Ventricular fibrillation or standstill was then induced by an overdose of barbiturate and the hearts were excised rapidly and placed in ice.

The right ventricle, epicardial fat, valve tissue, and chordae tendineae were cut away and the left atrium and adjoining vascular structures were separated from the left ventricle at the atrioventricular ring. The remaining left ventricle was rapidly frozen in liquid freon and sliced with a rotary blade into transverse sections 5 mm in thickness and allowed to thaw. The section containing the ultrasonic crystals was carefully dissected in order to expose the crystals. The section was photographed and then the thickness of the ventricular wall and the depth of the ultrasonic crystals within the ventricular wall were measured. The relationship between the lateral ultrasonic crystal and the edge of myocardium outlined by the methylene blue border was also recorded.

Clear glass plates were placed over both sides of all left ventricular sections; epicardial and endocardial outlines as well as the areas perfused and not perfused by methylene blue were traced on clear sheets of acetate under a ×10 magnifying lens. To visualize the infarcted tissue the slices were incubated in triphenyltetrazolium chloride (TTC) for 20 min at 37°C (14). Infarcted (white) and noninfarcted (deep red) areas on both sides of each slice were also traced on the acetate sheets. In the dogs subjected to 3 h of coronary occlusion followed by 72 h of reperfusion, two transverse slices from each left ventricle were also divided into ~15-mm wide transmural sections, stained with hematoxylin, eosin, and Masson trichrome, and examined microscopically to determine the location and quantity of necrotic tissue. The slides of stained tissue sections were placed in a photographic enlarger and the magnified (~×50) images of infarcted and noninfarcted tissue were traced as previously described (15). Necrosis was defined by the presence of clumping and coagulation of the myocardial fibers, pyknosis of the nuclei, obliteration of cross-striations, and more intense eosinophilia than in the nonnecrotic tissue. The following information was obtained by computation using values measured by a computerized electronic planimeter: (*a*) the area-at-risk for necrosis (A_r = ratio of all areas unstained by methylene blue to total areas of all slices); and (*b*) area of necrosis (A_n = ratio of all areas unstained by TTC to total areas of all slices, or in dogs subjected to 3 h of coronary occlusion, the ratio of the area of histologically infarcted tissue to total area). From these values the area of necrosis was expressed as a fraction of the area-at-risk by dividing A_n by A_r.

To determine whether the presence of flurbiprofen might possibly alter the staining characteristics of TTC, five additional dogs were subjected to 1-h coronary occlusions followed by 5 h of reperfusion. The left ventricles were sectioned as described previously and the cut surfaces of contiguous slices (identical infarct areas) were incubated separately, one in TTC alone, and the other in TTC plus flurbiprofen. The infarct areas were drawn, planimetered, and compared to ascertain whether any differences in the apparent size or staining of the infarcts was present.

Using the TTC-stained section containing the ultrasonic crystals with the acetate overlay of the area-at-risk as a guide, the left ventricular tissue was dissected for analysis of RMBF from five regions (Fig. 2): (*a*) a 5-mm wide transmural section of tissue that bisected the midmyocardial circumference of the area-at-risk (zone 1); (*b*) tissue at the lateral inner margin of the area-at-risk, but on the side opposite the ultrasonic crystals (zone 2); (*c*) a 3-mm wide strip of myocardial tissue between the ultrasonic crystals (zone 3) (two strips of tissue were cut in dogs with both subepicardial and subendocardial crystals); (*d*) methylene-blue stained tissue immediately adjacent to the lateral border of the area-at-risk (zone 4); and (*e*) normal myocardium distant from the area-at-risk (zone 5). Each of these sections was further divided into inner (subendocardial-half) and outer (subepicardial-half) portions except for the tissue from zone 3, which was left intact. The pieces of tissue were weighed and placed in a multichannel gamma well counter and counted in appropriately selected energy windows for 10 min. Values for RMBF and cardiac output were calculated as previously described (16, 17). In the dogs subjected to 3 h of coronary occlusion followed by 72 h of reperfusion, the degree of microsphere "washout" after 3 d was assessed by calculating the ratio of RMBF in noninfarcted tissue to RMBF in infarcted tissue as measured by microspheres injected before coronary occlusion (when the ratio should be 1:1), and then correcting the postocclusion values for RMBF in infarcted tissue by multiplying the value by the calculated ratio (1.1±0.03).

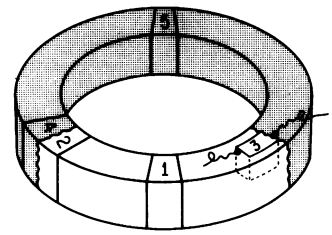

FIGURE 2 Diagram of a transverse section of left ventricular myocardium showing the five zones from which tissue was dissected for analysis of regional myocardial blood flow. Zone 1, transmural section of tissue from the center of the area-at-risk; zone 2, tissue at the lateral inner margin of the area-at-risk; zone 3, tissue between the ultrasonic crystals; zone 4, tissue immediately outside the lateral border of the area-at-risk; and zone 5, nonischemic myocardium distant from the area-at-risk. Stippled region represents tissue stained by methylene blue dye.

Statistical analyses. Student's *t* test was used to compare the values for each of the hemodynamic variables, RMBF, area-at-risk, and the area of necrosis in respective treated and control groups, and an analysis of variance for repeated measures (18) was used to compare values measured over time. A one-sample *t* test was used ($\alpha = 0.01$) for comparisons between preocclusion values to allow for multiple comparisons.

RESULTS

Of the 56 dogs entered in the study, 4 were excluded because of the development of ventricular fibrillation immediately after LAD occlusion and 4 because of ventricular fibrillation early during the reperfusion period, 2 each in the control and treated groups, respectively. Of the remaining 48 dogs, 25 were assigned at random to the treated group and 23 to the control group. Five dogs in each group had been subjected to 3 h of coronary occlusion followed by 72 h of reperfusion and the remainder to 1 h of coronary occlusion. The two groups were similar with respect to the total dose of barbiturate administered during the

TABLE I
Preocclusion of Hemodynamic Values in Treated and Control Dogs

	Control	Treated
Heart rate, *beats/min*	144±8	137±9
Mean arterial pressure, *mm Hg*	100±11	103±10
LVEDP, *mm Hg*	5.2±0.9	4.7±0.7
dP/dt at DP_{40}, *mm Hg/s*	1,842±186	1,915±192
Mean coronary flow, *ml/min*	59±7	63±5
EDL, *mm*		
Subendocardial segments (n = 10)	10.5±1.3	10.7±1.6
Midmyocardial segments (n = 28)	10.8±1.4	10.5±1.8
Subepicardial segments (n = 10)	10.3±1.4	10.6±1.7
%SS		
Subendocardial segments (n = 10)	16.7±1.9	17.6±2.3
Midmyocardial segments (n = 28)	18.5±1.5	17.8±2.2
Subepicardial segments (n = 10)	20.5±2.7	21.6±2.5
Peak *dSL/dt*, *mm/s*		
Subendocardial segments (n = 10)	16.4±3.0	17.0±1.8
Midmyocardial segments (n = 28)	17.9±2.9	17.8±2.4
Subepicardial segments (n = 10)	18.4±2.5	18.2±2.4

Values given are mean±SE. *dP/dt* at DP_{40} = time rate of change of pressure in the left ventricle at a developed pressure of 40 mm Hg.

experiment (controls = 30 mg/kg initially plus 7.9±1.6 mg/kg thereafter; treated = 30 mg/kg initially plus 7.3±2.4 mg/kg thereafter; P = NS) and the total dose of lidocaine administered (controls = 63.5±7.8 mg; treated = 67.5±7.3 mg; P = NS). Preocclusion values for body weight, heart rate, mean arterial pressure, LVEDP, *dP/dt* at a developed pressure of 40 mm Hg, mean coronary flow, EDL, %SS, and peak *dSL/dt* were not statistically different between treated and control dogs (Table I).

Hemodynamic changes during 1 and 3 h of coronary occlusion

Similar changes in hemodynamic variables occurred in the two groups immediately after coronary occlusion. The myocardial segments subtended by the ultrasonic crystals changed from active shortening to passive lengthening within 30 s following occlusion of the LAD. *dP/dt* decreased and LVEDP increased immediately after LAD occlusion but recovered partially toward preocclusion values by the end of 1 h of coronary occlusion period (Table II). No further significant change occurred in dogs subjected to 3 h of coronary occlusion. The administration of flurbiprofen was not associated with any changes in regional or global performance, as occurs with agents with a known positive inotropic effect. Thus, the differences in regional function between control and treated dogs during reperfusion were not the result of a direct positive inotropic effect of the drug.

Changes in regional function during reperfusion after 1 h of coronary occlusion

Both the rate of recovery of active shortening in the ischemic segments (Fig. 3) and the degree of hyperemic coronary flow during reperfusion differed between treated and control groups.

Subendocardial segments. In control dogs systolic passive lengthening of the previously ischemic seg-

TABLE II
Selected Hemodynamic Values 30 s and 1 h after Coronary Artery Occlusion

	Control		Treated	
	30 s	1 h	30 s	1 h
EDL, *mm*				
Subendocardial segments (n = 10)	13.1±2.1	12.2±2.3	13.3±2.0	12.5±2.6
Midmyocardial segments (n = 28)	12.4±1.9	11.7±2.0	12.2±2.3	11.4±1.7
Subepicardial segments (n = 10)	12.0±2.1	11.7±1.9	12.1±2.3	10.9±1.8
%SS				
Subendocardial segments (n = 10)	−24.8±4.1	−22.6±3.6	−23.6±3.0	−22.2±3.4
Midmyocardial segments (n = 28)	−22.6±4.2	−18.8±3.9	−23.1±3.9	−19.8±3.0
Subepicardial segments (n = 10)	−19.8±2.1	−19.6±2.0	−20.2±2.3	+9.8±1.3
LVEDP, *mm Hg*	8.4±2.0	7.3±1.9	7.9±1.8	6.9±1.5
LV *dP/dt* at DP_{40}, *mm Hg/s*	1,612±160	1,725±182	1,664±210	1,771±185

Values given are mean±SE. A negative value for %SS signifies segment lengthening (paradoxical expansion) during systole.

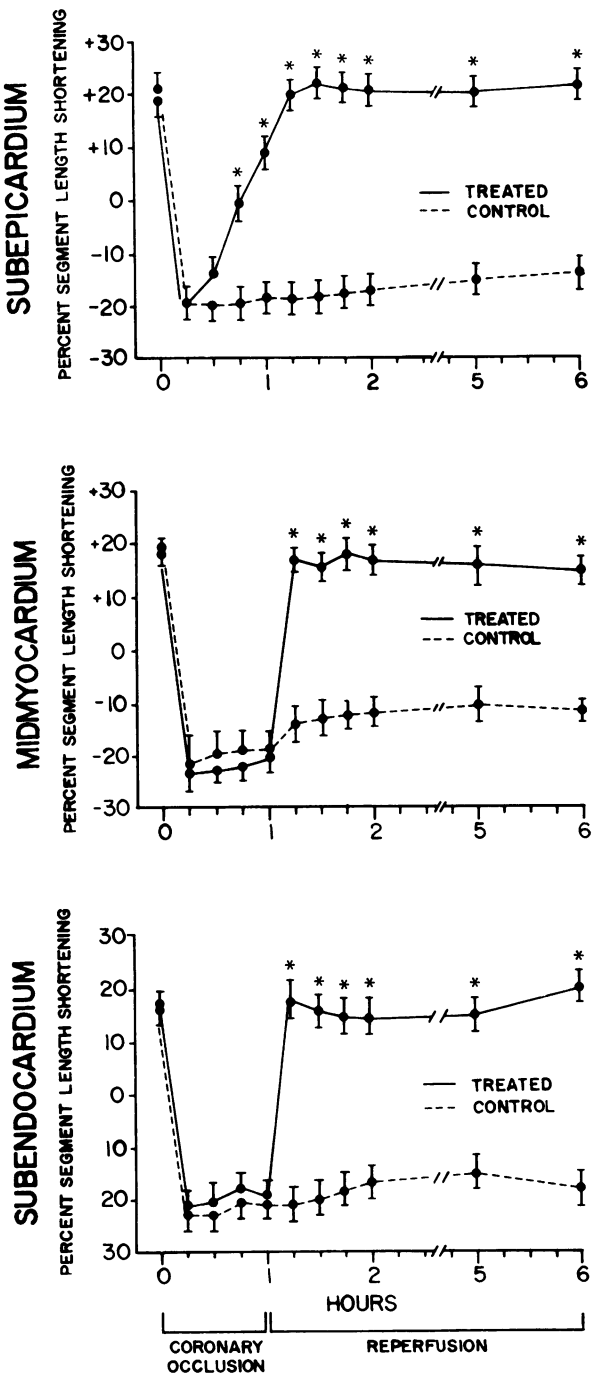

FIGURE 3 Separate graphs showing %SS in the subepicardium, midmyocardium, and subendocardium of control and treated dogs during 1 h of coronary occlusion and 5 h of reperfusion. Active systolic shortening values are represented by positive numbers on the ordinate and systolic passive lengthening values by negative numbers. Regional function was different between control and treated dogs only during reperfusion in the previously ischemic subendocardial and midmyocardial segments, but improvement in function began to occur in the subepicardium of treated dogs even while the coronary artery was still occluded, and became significantly different from control within 30 min of the time of drug administration. Values shown are mean±SEM for each time period. *, statistically different from respective value in control dogs ($P < 0.01$).

ments persisted during the 5-h reperfusion period (1 h of occlusion, %SS = −22.6±3.5%; 5 h of reperfusion = −20.9±3.2%; P = NS) (Fig. 4). In flurbiprofen-treated dogs active shortening of the previously ischemic segments was restored following 1 min of reperfusion (Fig. 5), returned to preocclusion values within 5 min of reperfusion, and did not deteriorate thereafter for the remaining 5 h, although peak *dSL/dt* remained slightly depressed (14.9±1.9 mm/s) compared with preocclusion values (17.2±1.9 mm/s; $P < 0.05$).

Midmyocardial segments. Systolic lengthening also persisted for the full 5 h of reperfusion in the midmyocardial segments of control dogs (Fig. 6) (1 h of occlusion, %SS = −18.8±3.9%; 5 h of reperfusion = −16.7±3.5%; P = NS). The rate of recovery of systolic shortening in flurbiprofen-treated dogs during reperfusion was rapid (Fig. 7), as observed in the subendocardial segments (1 h of occlusion, %SS = −19.8 ±3.0%; 5 min reperfusion = +17.9±2.3%; $P < 0.001$ compared with midmyocardial segments in control dogs) and also did not deteriorate over the 5-h period of reperfusion. As with the subendocardial segments, peak *dSL/dt* remained slightly depressed in the flurbiprofen-treated group at 5 h of reperfusion (11.4±2.2 mm/s) compared with preocclusion values (17.8±2.4 mm/s; $P < 0.01$).

Subepicardial segments. In control dogs, the lack of recovery of regional function in the subepicardium was similar to that observed during reperfusion in subendocardial and midmyocardial segments (Fig. 4) (1 h of occlusion, %SS = −19.6±2.0%; 5 h reperfusion = −16.5±3.8%; P = NS). In flurbiprofen-treated dogs the rate of recovery was different from that in deeper segments because recovery of some degree of systolic shortening (Table II) occurred even during the 1-h occlusion period (Fig. 5). This recovery during occlusion was not observed in control dogs nor in the subendocardial or midmyocardial segments of flurbiprofen-treated dogs. Thus, although there was full recovery of regional function within 5 min of reperfusion, part of this had occurred before release of the coronary clamp (1 h of occlusion, %SS = +9.8±1.3%; 5 min reperfusion = +20.8±2.9%; $P < 0.001$, compared with subepicardial segments in control dogs). In addition, peak *dSL/dt* returned to preocclusion values within 5 min of reperfusion (preocclusion peak *dSL/dt* = 18.0±2.0 mm/s; 5 min of reperfusion = 18.3±2.6 mm/s).

In control dogs maximum hyperemic coronary flow

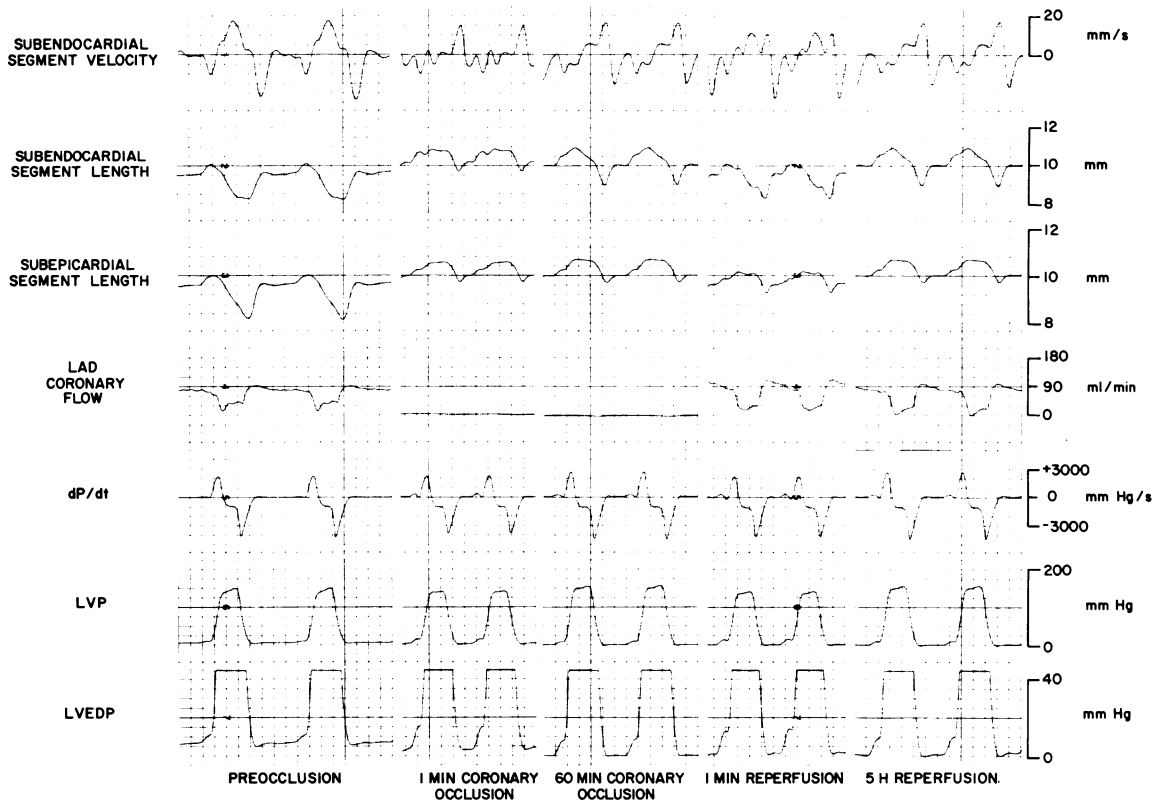

FIGURE 4 Representative tracings from a control dog showing subendocardial segment velocity and length, subepicardial segment length, pulsatile LAD coronary flow, *dP/dt* of left ventricular pressure (LVP), and LVEDP before coronary occlusion, at 1 and 60 min after coronary occlusion and after 1 min and 5 h of reperfusion. Although there was a slight improvement in regional function at both sites after 1 min of reperfusion, this was not sustained. After 5 h of reperfusion, regional function was not different from that during coronary occlusion, despite the return to preocclusion LAD coronary flow. There is an absence of hyperemic coronary flow after 1 min of reperfusion.

was 92±9 ml/min, which was 146±11% of the mean coronary flow value during the preocclusion period (63±8 ml/min). In contrast, maximum hyperemic coronary flow was 140±13 ml/min in flurbiprofen-treated dogs, which was 233±21% of mean preocclusion coronary flow (60±7 ml/min) (Fig. 8). This difference in maximum hyperemic coronary flow, which was significant ($P < 0.01$), occurred at similar coronary perfusion pressures in treated and control dogs, which suggests that the resistance of the coronary bed was lower in flurbiprofen-treated dogs than in control dogs during the early reperfusion period. In fact, using values for mean diastolic arterial pressure and mean coronary flow to calculate the resistance of the coronary bed at the time of maximum hyperemic coronary flow, we found that coronary bed resistance was considerably lower in treated dogs (50.9±3.8 dyn·s·cm^{-5}) than in controls (81.8±6.6 dyn·s·cm^{-5}) ($P < 0.01$). The approximate nature of this calculation is appreciated because the perfusion pressure in the arterioles differs from that in the aorta.

Changes in regional function during reperfusion after 3 h of coronary occlusion

Subendocardial segments. In control dogs systolic passive lengthening of the previously ischemic segments persisted for the entire 72-h period of reperfusion. In fact, values for the percent of systolic lengthening were not significantly different after 72 h of reperfusion from those after 3 h of coronary occlusion (Fig. 9). In flurbiprofen-treated dogs subjected to 3 h of coronary occlusion the return of active shortening in the previously ischemic segments occurred at a slower rate than occurred after a 1-h occlusion in treated dogs, but even this slower rate of recovery was significantly different from that in the control group (Fig. 9). After 5 min of reperfusion, %SS was 6.2±0.9%,

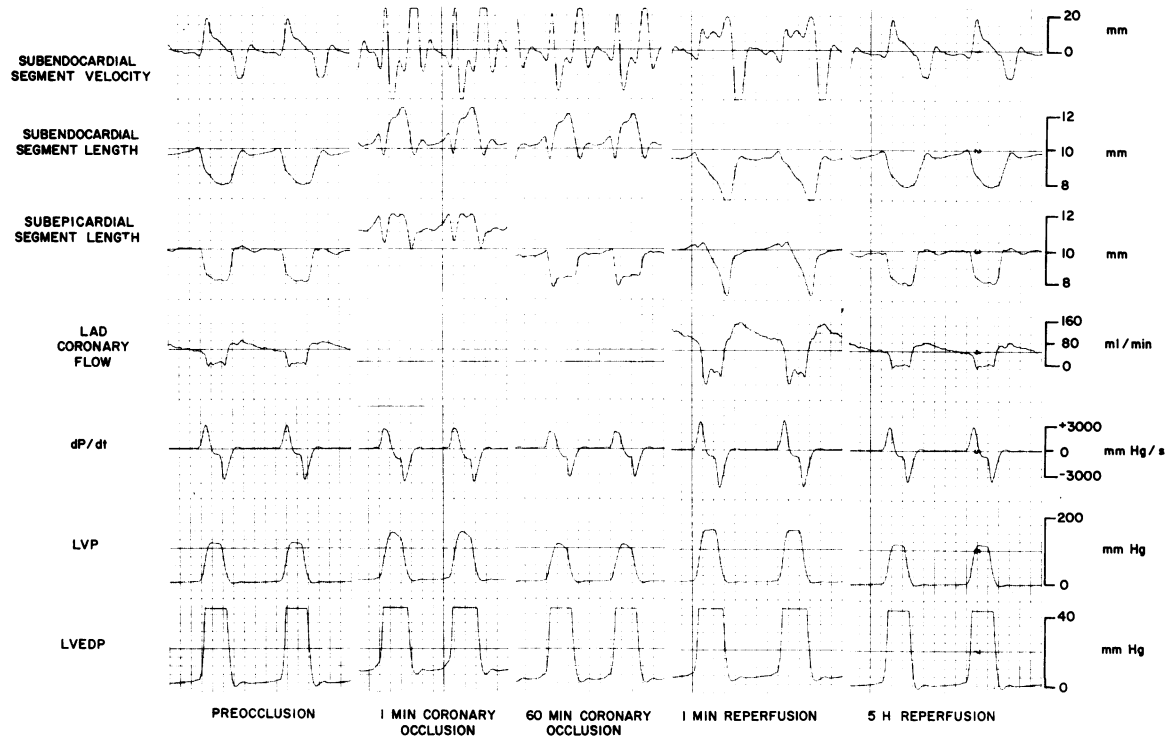

FIGURE 5 Regional function in the subendocardium and subepicardium of a treated dog. 1 min after coronary occlusion both regions underwent systolic passive lengthening. After 60 min systolic passive lengthening was present to the same degree in the subendocardium, but the subepicardium returned to near normal function. After 1 min of reperfusion the period of hyperemic coronary flow was associated with an "overshoot" in the extent of shortening in both regions and after 5 h of reperfusion, regional function was not significantly different from what it was before occlusion.

but improved to 8.8±2.4% after 48 h, and to 12.7±2.8% after 72 h of reperfusion. The latter value represented a significant ($P < 0.01$) improvement in regional function when compared with the control group after 72 h of reperfusion.

Subepicardial segments. In control dogs there was a small but significant amount of improvement in regional function in the subepicardial segments by the end of 72 h of reperfusion (Fig. 9), although the %SS was still significantly depressed (8.9±1.1%) compared with preocclusion (18.9±2.1%; $P < 0.01$). In flurbiprofen-treated dogs a small amount of systolic shortening occurred within 15 min of the infusion of flurbiprofen and persisted for the 3-h period of coronary occlusion. In contrast to the flurbiprofen-treated dogs subjected to only 1 h of coronary occlusion, complete recovery of regional function did not occur within 5 min of reperfusion; recovery occurred slowly but was complete after the first 24 h of reperfusion so that %SS (18.1±2.3%) and peak *dSL/dt* (18.4±2.0 mm/s) were not significantly different from preocclusion values (preocclusion %SS = 18.5±2.6%; peak *dSL/dt* = 18.1 ±2.5 mm/s).

Changes in global function during reperfusion after 1 h of coronary occlusion

In control dogs the left ventricular end-diastolic pressure was actually higher after 5 h of reperfusion (9.8 ±2.1 mm Hg) than it was at the end of the 1-h coronary occlusion period (7.3±1.9; $P < 0.01$). The value for *dP/dt* at developed pressure of 40 mm (DP_{40}) was slightly (but not significantly) lower after 5 h of reperfusion (1,684±165 mm Hg/s) than it was after 1 h of coronary occlusion (1,725±182 mm Hg/s). In flurbiprofen-treated dogs the LVEDP returned to preocclusion values by 5 h of reperfusion (LVEDP preocclusion = 4.6±0.9 mm Hg; after 1 h coronary occlusion = 6.9±1.5 mm Hg; after 5 h of reperfusion = 4.8±1.0 mm Hg). The *dP/dt* at DP_{40} at the end of 5 h of reperfusion (1,892±165 mm Hg/s) was not significantly different from the preocclusion value (1,906 ±165 mm

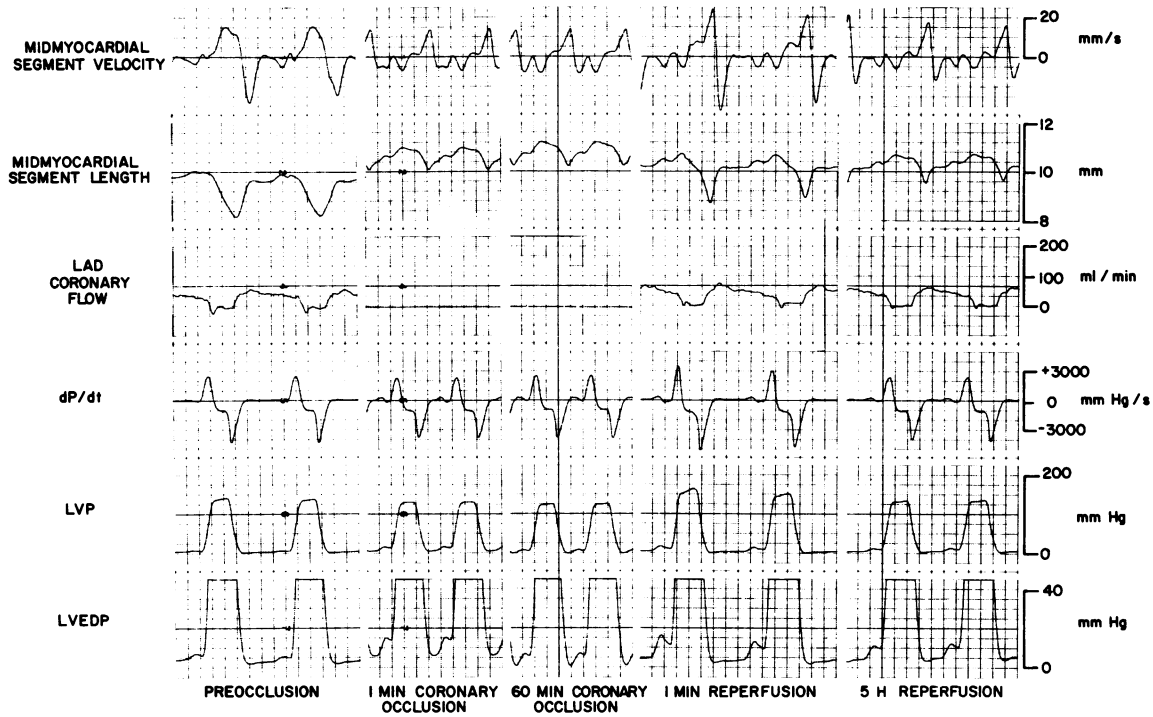

FIGURE 6 Regional function in the midmyocardium of a control dog. After 1 min of reperfusion there was only a slight increase in coronary flow associated with a transient period of improved regional function, both of which have disappeared after 5 h of reperfusion.

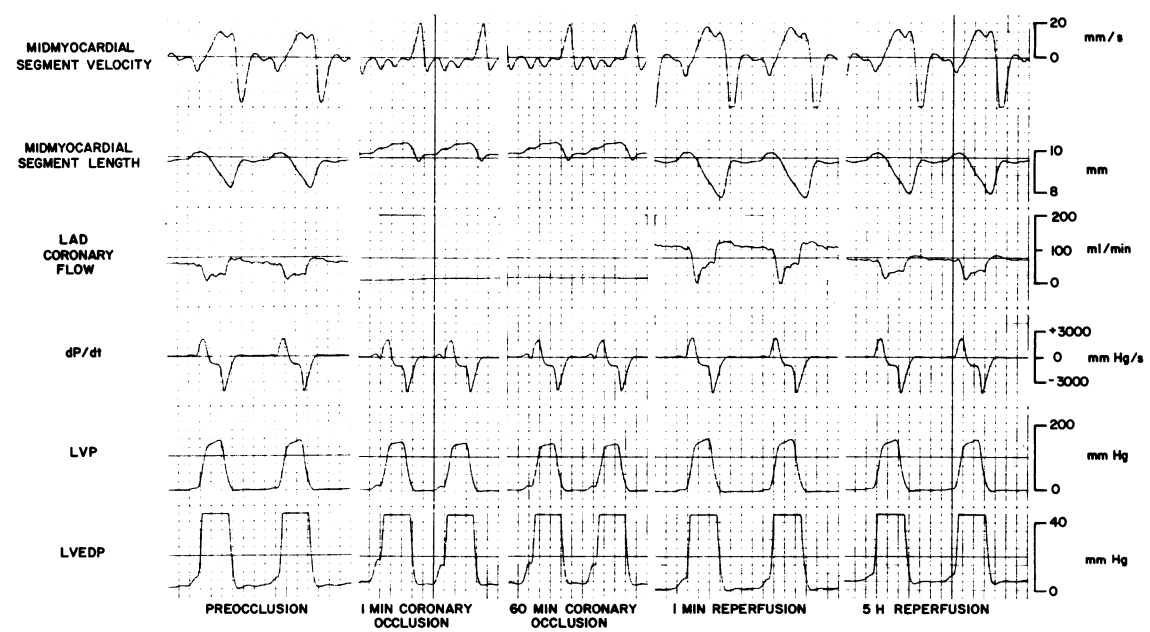

FIGURE 7 Regional function in the midmyocardium of a treated dog. After 1 min of reperfusion hyperemic coronary flow was associated with an overshoot in the extent of myocardial shortening and after 5 h of reperfusion there was no difference in coronary flow or regional function compared with preocclusion values.

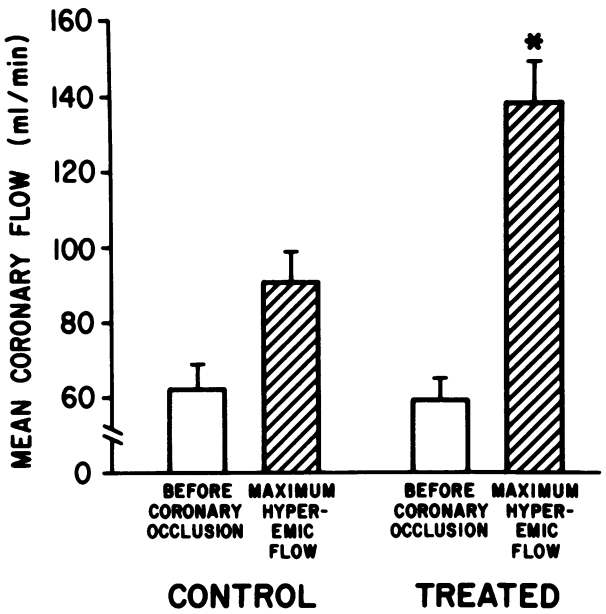

FIGURE 8 Mean coronary flow values (mean±SEM) before coronary occlusion and during maximum hyperemic coronary flow. *, statistically different from value in control group ($P < 0.01$).

Hg/s), although it had decreased considerably after 1 h of coronary occlusion (1,771±185 mm Hg/s) as it did in control dogs.

Changes in global function during reperfusion after 3 h of coronary occlusion

In control dogs the LVEDP was 8.9±1.6 mm Hg at the end of the 3-h coronary occlusion period, increased to 11.7±2.3 mm Hg ($P < 0.01$, compared with preocclusion value), and remained elevated (10.5 ±2.1 mm Hg; $P < 0.01$) after 72 h of reperfusion. The value for *dP/dt* at DP_{40} was not significantly improved after 72 h of reperfusion (1,652±186 mm Hg/s) when compared with the value at the end of the 3-h period of coronary occlusion (1,621±195 mm Hg/s), and was still depressed when compared with the preocclusion value (1,984±187 mm Hg/s; $P < 0.05$). In flurbiprofen-treated dogs the LVEDP returned to preocclusion value after 72 h of reperfusion (preocclusion = 4.8±0.8 mm Hg; 72 h reperfusion = 5.1 ±0.9 mm Hg; P = NS), representing a significant difference from the control group ($P < 0.01$, compared with control). The value for *dP/dt* at DP_{40} returned to preocclusion value (preocclusion = 1,963±198 mm Hg/s) after 24 h of reperfusion (1,904±200 mm Hg/s) and also represented a significant improvement compared with control ($P < 0.01$).

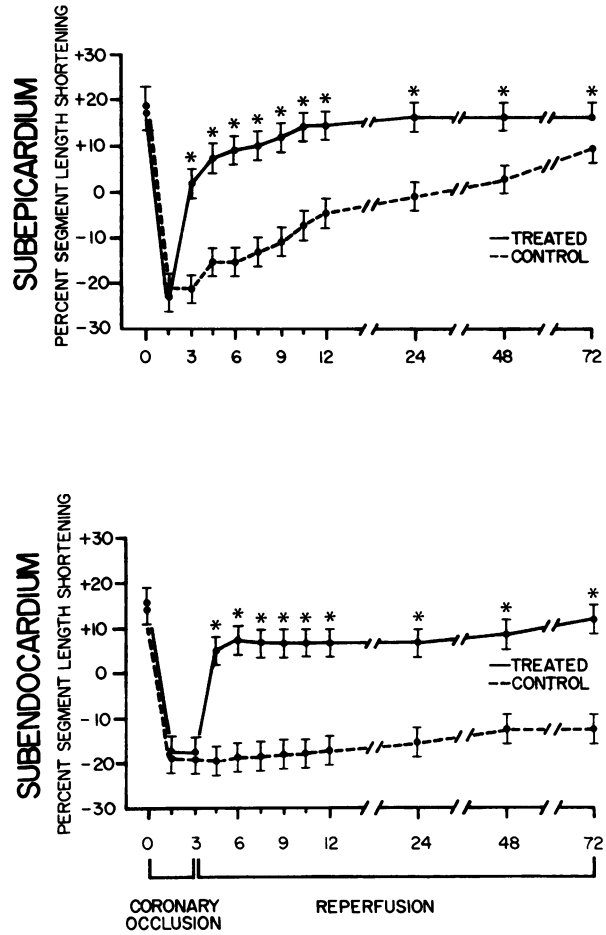

FIGURE 9 %SS in the subepicardium and subendocardium of control and treated dogs during 3 h of coronary occlusion followed by 72 h of reperfusion. Values shown are mean±SEM for each time period. *, statistically different from respective value in control dogs ($P < 0.01$).

Location of ultrasonic crystals and RMBF

It was deemed important to ascertain whether the placement of the ultrasonic crystals was relatively uniform with respect to both the lateral border of the ischemic bed and the depth within the myocardium, because differences in placement alone could account for variations in segment function. For example, myocardial segments nearer the central region of the ischemic bed or closer to the endocardium might be expected to have lower values for RMBF during coronary occlusion than segments nearer the ischemic border or closer to the subepicardium. It is also possible that the rate of recovery of active shortening during reperfusion would be slower in segments with lower values for RMBF during coronary occlusion. The location of the crystals at postmortem examination,

however, was not significantly different between control and treated dogs (in comparisons of similar sites, i.e., midmyocardium with midmyocardium, etc.) with respect to either lateral orientation or transmural depth.

Furthermore, values for RMBF within the ischemic segments of control dogs during 1 h of coronary occlusion (0.33±0.04 ml/min per g) were not different from RMBF values in treated dogs (0.35±0.03 ml/min per g; P = NS). The values for RMBF in the other four zones were also similar in these two groups of dogs (Table III). In the same two groups of dogs after 5 h of reperfusion, RMBF in zones 1 through 4 returned to values that were not statistically different from values in normal myocardium (zone 5) except for the endocardial portion of zone 1 in control dogs. Even with 5 h of reperfusion, RMBF increased to an average of only 58% of the value in normal tissue and was statistically different ($P < 0.05$) from RMBF in the same region in treated dogs. Because the endocardial portion of zone 1 in control dogs always contained some necrotic tissue, it is likely that the decreased RMBF in this region represents a "no-reflow" phenomenon (11).

In dogs subjected to 3 h of coronary occlusion, RMBF in the tissue between the subendocardial ultrasonic crystals also was not significantly different between control dogs (0.34±0.04 ml/min per g) and dogs treated with flurbiprofen (0.32±0.05 ml/min per g; P = NS). After 72 h of reperfusion, RMBF in the tissue in the endocardial portion of zone 1 was only 0.51±0.03 ml/min per g in control dogs and 0.68±0.05 ml/min per g ($P < 0.05$) in treated dogs, which suggests that a zone of no-reflow was present in both groups, although it was slightly more severe in the control dogs.

Myocardial necrosis

The quantity of myocardium-at-risk expressed as a percentage of total left ventricle was similar in treated (29.2±2.6%) and control dogs (28.1±2.2%; P = NS) subjected to 1 h of coronary occlusion. In control dogs, however, 17.9±1.8% of the myocardium-at-risk became necrotic compared with 0% necrosis in flurbiprofen-treated dogs. In control dogs the necrotic tissue occupied the most subendocardial portion of the area-at-risk and in none did it extend to the region between the ultrasonic crystals, and in fact was always at least 3 mm away from the crystal positioned within the ischemic bed (Fig. 10).

In dogs subjected to 3 h of coronary occlusion, the quantity of myocardium-at-risk was also similar in control (27.2±2.3%) and treated (28.2±2.5%; P = NS) groups. In the control group, 65.3±6.8% of the myocardium-at-risk became necrotic; this was significantly greater ($P < 0.01$) than in the treated group in which only 36.7±3.5% of the myocardium-at-risk became necrotic. In these two groups of dogs, the amount of necrotic tissue was assessed from wholemount specimens by light microscopy and standard histological criteria, although the values for infarct size as assessed by TTC staining were not significantly different from those obtained by histological examination (Fig. 11).

TABLE III
RMBF 15 min after Coronary Occlusion and after 5 hours of Perfusion in Dogs Subjected to 1 h of Coronary Occlusion

		Control		Treated	
		15 min after coronary occlusion	After 5 h of reperfusion	15 min after coronary occlusion	After 5 h of reperfusion
Zone 1	Epicardial	0.17±0.03	1.05±0.06	0.25±0.02	0.96±0.07
	Endocardial	0.11±0.02	0.63±0.05	0.15±0.03	0.95±0.08*
Zone 2	Epicardial	0.34±0.03	1.03±0.07	0.33±0.05	1.01±0.09
	Endocardial	0.32±0.03	1.01±0.08	0.28±0.04	0.98±0.07
Zone 3	Subendocardial	0.30±0.05	0.97±0.06	0.31±0.03	0.96±0.05
	Midmyocardial	0.34±0.03	1.03±0.05	0.36±0.02	1.06±0.06
	Subepicardial	0.36±0.02	1.04±0.07	0.35±0.03	1.03±0.05
Zone 4	Epicardial	0.66±0.04	1.04±0.05	0.64±0.03	1.04±0.06
	Endocardial	0.63±0.05	1.03±0.06	0.58±0.03	1.02±0.03
Zone 5	Epicardial	1.10±0.07	1.08±0.06	1.08±0.09	1.12±0.10
	Endocardial	1.04±0.05	1.07±0.03	1.03±0.06	1.07±0.05

* Statistically different ($P < 0.05$; Student's t test) from value for RMBF (endocardial portion) in zone 1 after 5 h of reperfusion in control dogs. Values are mean±SEM.

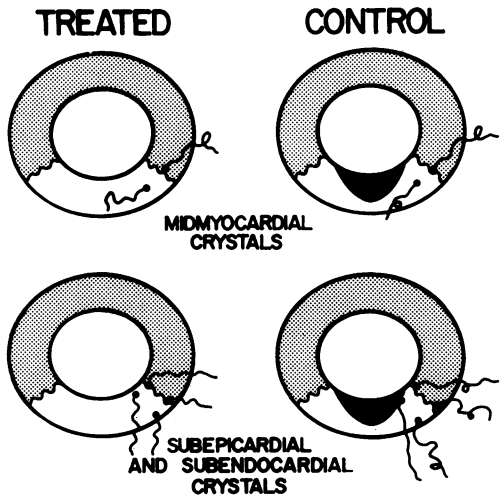

FIGURE 10 Diagrammatic representation of nonischemic methylene blue perfused myocardium (stippled region), the ischemic area-at-risk (nonstippled regions), the area of necrosis (black) and the placement of the ultrasonic crystals in transverse left ventricular sections of treated and control dogs subjected to 1 h of coronary occlusion.

In control dogs the tissue between the subendocardial ultrasonic crystals was completely infarcted. In treated dogs the same region of tissue showed only "patchy" areas of necrosis which occupied <10% of the region but was impossible to quantify accurately because of its patchy nature. Tissue between the subepicardial crystals was free from infarction in both groups of dogs.

In the five additional experiments to determine whether flurbiprofen had any effect on TTC staining, the quantity of necrotic tissue was not significantly different between contiguous surfaces of left ventricular tissue; thus, the differences in infarct size as evaluated by TTC in control and treated dogs subjected to 1 h of coronary occlusion were not the result of an alteration in the staining characteristics of TTC induced by flurbiprofen because flurbiprofen had no effect on TTC staining.

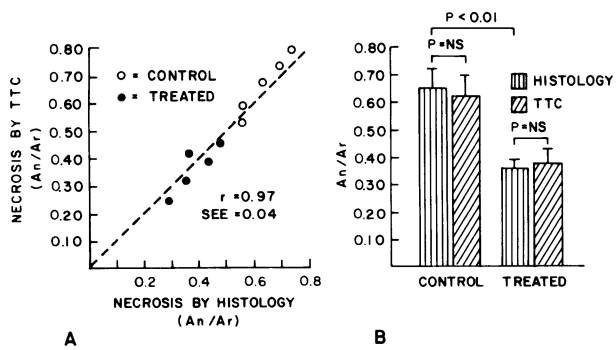

FIGURE 11 (A) Values for the area of necrosis (An) expressed as a fraction of the area-at-risk (Ar) as determined by TTC staining plotted against respective values determined by histological methods. SEE, standard error of the estimate. (B) Values (mean±SEM) for An/Ar in control and treated groups as determined by TTC staining and histological examination.

DISCUSSION

The extent and distribution of infarcted myocardial tissue after coronary occlusion is related to eventual morbidity, mortality, and cardiac function in patients with ischemic heart disease (19, 20). Immediately outside the central region of necrosis is an area of reversibly injured tissue that has the greatest potential for salvage by agents administered early in the course of myocardial infarction or by myocardial reperfusion. But the development of methods for reducing the severity of ventricular dysfunction during ischemia depends not only on the ability to prevent the central necrotic region from extending outward into the reversibly injured tissue (15), but also on the efficacy of interventions to preserve the function of the salvageable tissue long enough to allow the restoration of normal or near-normal blood flow to this region.

Previous studies in our laboratory have shown that flurbiprofen prevents a significant portion of the ischemic myocardium-at-risk for necrosis from becoming necrotic following a sustained 6-h coronary artery occlusion (10). The results of the present study suggest that in control dogs, grossly normal, nonnecrotic tissue salvaged by reperfusion contracted abnormally during 5 h of reperfusion after a 60-min period of coronary occlusion, whereas, in dogs treated with flurbiprofen, equally ischemic tissue also salvaged by reperfusion recovered near-normal contractile function within 5 min of reperfusion. Furthermore, in control dogs subjected to 3 h of coronary occlusion there was no improvement in function after 72 h of reperfusion in subendocardial segments, most likely a result of infarction of the tissue. In treated dogs there was a significant degree of improvement in regional function in subendocardial tissue with a small quantity of patchy necrosis after 72 h of reperfusion, although recovery was incomplete. There was also significantly greater recovery of function in subepicardial tissue in treated dogs when compared with the control dogs, although none of this tissue was necrotic in either group.

The functional characteristics of ischemic tissue following permanent coronary occlusions have been described for myocardial infarctions in conscious dogs (5). Both moderately and severely ischemic tissue exhibit functional deterioration within minutes of coronary artery occlusion. Some segments undergo further functional deterioration between 24 h and 1 wk after coronary occlusion. Thus, it appears that the function of ischemic myocardial segments remains depressed following coronary artery occlusion and shows a re-

duced ability to shorten or contract in tissue mildly to moderately ischemic, and that frankly paradoxical motion occurs in severely ischemic tissue with no evidence of recovery for a full week after occlusion.

The most direct method of salvaging ischemic but viable myocardium is reperfusion, because it supplies both oxygen and metabolic substrates to reperfusable myocardial tissue in sufficient quantity to sustain life in reversibly injured cells (21, 22). The time at which reperfusion of ischemic tissue occurs, however, is important in determining its ability to maintain myocardial cell integrity and segmental myocardial function (11). Pagani et al. (6) followed the changes in left ventricular dynamics induced by brief (100 s) periods of either global or regional ischemia and subsequent reperfusion in conscious dogs. It was observed in both types of ischemic insult that the extent of shortening of myocardial segments was reduced more rapidly and greatly than was the velocity of shortening, and that with localized ischemia segment work (calculated from the areas of the pressure-length loops) was reduced even more than was shortening. With reperfusion, a transient overshoot in function above preischemic control levels was observed after either global or regional ischemia, and was directly related to the degree of associated reactive hyperemia. It may be presumed that any process that inhibits reactive hyperemia after coronary occlusion and release will also interfere with the contractile function of the tissue supplied by the occluded coronary artery. Conversely, agents that tend to preserve reactive hyperemia may additionally preserve myocardial segment function in this manner.

5–15-min periods of coronary occlusion and reperfusion have also been examined in the conscious dog model. Heyndrickx et al. (7) found that a 5-min occlusion depressed overall left ventricular function transiently, but that just before release of the occlusion overall function had returned to a near-normal level. Regional function in the ischemic zone, however, remained markedly depressed, with absence of shortening or even paradoxical systolic expansion persisting for over 3 h of reperfusion. 15-min coronary occlusions resulted in derangement of function of the ischemic zone, which exceeded 6 h. These observations indicate that even relatively brief periods of myocardial ischemia result in prolonged periods of mechanical dysfunction, even when regional blood flow is restored to normal levels after release of the occlusion.

Extended periods of myocardial ischemia followed by longer periods of reperfusion have been examined for recovery of myocardial function. Theroux et al. (23) followed regional myocardial function and dimensions during 2 h of coronary occlusion followed by 4 wk of reperfusion. They found that ischemic segments tended to show only slight functional improvement soon after reperfusion, but that in succeeding weeks, progressive decreases in EDL and some further improvement in shortening occurred. In marginally ischemic segments, shortening remained depressed during the early reperfusion period but returned to normal values by 4 wk. In contrast, five similarly studied dogs subjected to permanent coronary occlusion showed considerably less recovery of function in both marginal and ischemic segments. Thus, it appears from previous studies that despite the ostensibly beneficial effects of reperfusion after coronary occlusions lasting 15–120 min, function in ischemic myocardial segments recovers relatively slowly, becoming normal sometime between 3 h and 4 wk after release of the occlusion.

In accord with the observations summarized above, the control dogs in our experiments subjected to a 1-h coronary occlusion showed relatively little recovery of function in ischemic myocardial segments during 5 h of reperfusion. But the return of active shortening to preocclusion values within 5 min of reperfusion in dogs treated with flurbiprofen represents a markedly accelerated rate of recovery. This difference in the rate of functional recovery is not likely due to the absence of necrosis in treated dogs, since in control dogs not only was the total quantity of necrotic tissue relatively small, but it was always located at a distance from the ischemic myocardium being evaluated. A more rigorous comparison was provided by the 3-h coronary occlusions in which the dogs treated with flurbiprofen showed significantly more rapid recovery of function than did control dogs.

A number of agents or interventions have been shown to improve the function of ischemic myocardial tissue during brief or sustained coronary occlusions. These include oubain (24), the combination of propranolol and oubain (25), hypothermia (26), nitroglycerin (27), and nitroprusside (27). It has also been shown that greater left ventricular wall tension can be developed during reperfusion in dogs respiring high levels of inspired oxygen during coronary occlusion than in dogs respiring room air (28). In our study there were no differences in regional function during coronary occlusion in the dogs receiving flurbiprofen and in control dogs treated with saline, except in the subepicardial segments of treated dogs, in which there was a return of active shortening even before reperfusion. This may have been due to the selective availability of the drug to the ischemic subepicardium, which has the highest levels of RMBF during occlusion. Moreover, flurbiprofen itself did not produce any immediate hemodynamic effects or changes in regional myocardial blood flow during occlusion. The differences in regional function in the subendocardium and midmyocardium occurred only during the period of reperfusion. Since reactive hyperemia was

greater in flurbiprofen-treated dogs than in control dogs after the release of the coronary occlusion, it seems likely that the rapid recovery of regional function was modulated, at least in part, by RMBF during early reperfusion and therefore by the resistance of the coronary perfusion bed. This difference in the resistance of the perfusion bed in treated dogs could be related to differences in either intravascular (capillary integrity) or extravascular (interstitial edema) factors. The greater reactive hyperemia was not a consequence of the augmented contractile function observed in flurbiprofen-treated dogs during reperfusion, because studies with the coronary bed maximally dilated have shown that myocardial contractility is a major component of extravascular coronary resistance and is a mechanical determinant of regional coronary blood flow and its transmural distribution (29); that is, an increase in myocardial contractility during maximal coronary dilatation causes a reduction in blood flow to the same tissue.

Thus, in the present study it appears that flurbiprofen treatment was associated with greater reactive hyperemia and increased regional performance during early reperfusion and that either the increase in RMBF modulated the increased contractile function or both were independently improved. Flurbiprofen appears to inhibit the cellular inflammatory response to ischemia and the production of certain inflammation-augmenting prostaglandins, and to decrease platelet aggregation (30). Although no conclusive evidence is currently available, flurbiprofen may also protect the integrity of the capillary walls in ischemic tissue. The mechanism by which it caused a rapid recovery of regional function during reperfusion is probably a combination of these properties, but appears to be independent of its effect on decreasing infarct size.

The present study lends support to the hypothesis that there are regions of functionally depressed myocardium surrounding irreversibly injured tissue with the potential for recovery of nearly normal contractility if an effective intervention is administered early enough after coronary artery occlusion. Future studies utilizing various interventions to protect ischemic myocardium from necrosis should certainly include an assessment of the preservation of regional ventricular function.

It must be emphasized that coronary occlusions in this study were followed by reperfusion and that the effects of flurbiprofen on the regional performance of ischemic myocardium during permanent coronary occlusions are unknown. However, the 1- and 3-h coronary occlusion models have considerable clinical relevance since many patients are being considered for early saphenous vein bypass graft surgery or intracoronary administration of streptokinase during which the patient may require preliminary myocardial protection for only a few hours (13). Both these techniques can be offered to the patient only after he or she reaches the hospital, and may be delayed while the necessary preparations are made to ensure that the procedures are carried out as successfully as possible. The observation that the administration of flurbiprofen followed by reperfusion resulted in less myocardial damage and earlier recovery of function than reperfusion alone, suggests that this agent may be used to provide protection as soon as the patient reaches a medical care facility, and during the necessary few hours until myocardial perfusion can be restored. By delaying the progression of myocardial necrosis in severely ischemic tissue, flurbiprofen may allow a greater portion of the heart to be salvaged by reperfusion.

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