Effects of Isoproterenol on Regional Myocardial Function, Electrogram, and Blood Flow in Conscious Dogs with Myocardial Ischemia

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ABSTRACT The effects of coronary occlusion and of subsequent isoproterenol infusion were examined in conscious dogs. Left ventricular (LV) function was assessed by measurements of LV diameter, pressure, velocity and dP/dt/P, and regional myocardial function was assessed by measurements of segment length (SL) and velocity of SL shortening in normal, border, and ischemic zones. Regional myocardial function was measured from the same sites, along with intramyocardial electrograms and regional myocardial blood flow as determined by radioactive microspheres. Coronary occlusion resulted in graded loss of function from the normal to severely ischemic zones with graded flow reductions and graded increases in ST segment elevation. Isoproterenol improved overall LV function, and function in the normal zone. Isoproterenol also improved function in 19 of 21 border-zone segments and in all moderately ischemic segments, while elevating further the ST segments. These changes were accompanied by increases in myocardial blood flow. In contrast, in severely ischemic segments, isoproterenol resulted in a deterioration of function, in that paradoxical motion occurred in segments previously akinetic during systole, while paradoxical motion was intensified in those segments in which it was already present. These changes were accompanied by further ST segment elevation but not by concurrent increases in blood flow. In addition, in 2 of 21 border zone segments, myocardial blood flow fell and these segments responded to isoproterenol with complete loss of function; paradoxical motion developed. Thus, in the conscious dog, a strong inotropic agent can improve function, even in the ischemic myocardium, as long as the required additional blood flow can be provided either through primary or collateral channels.

INTRODUCTION

Isoproterenol's potent inotropic and chronotropic actions enhance normal myocardial function at the expense of elevating myocardial oxygen consumption, and consequently, coronary blood flow. When isoproterenol is administered in the presence of global myocardial ischemia, a situation in which the entire myocardium is perfused inadequately, a paradoxical effect occurs, i.e., myocardial function deteriorates rapidly (1, 2). The effects of isoproterenol on myocardial function in the presence of regional ischemia, where the myocardium is perfused heterogeneously, are more complex. Study of this problem is further complicated because most current techniques are designed to evaluate overall left ventricular (LV) [1] performance and do not accurately characterize discrete changes in function in the different portions of the myocardium, i.e., the normal, border, and ischemic zones.

To investigate this problem, measurements of regional myocardial function were correlated with regional electrograms and regional perfusion in the presence of acute

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[1] *Abbreviations used in this paper:* D, diameter; dD/dt, rate of change of diameter; dP/dt, rate of change of pressure; LV, left ventricle; P, pressure; SI, segment length; V, velocity of shortening.

ischemia. Since general anesthesia and the trauma of operation affect myocardial function substantially (3, 4), the animals were studied in the conscious state several weeks after recovery from operation. The specific goals of this study included the examination of the effects of isoproterenol on the normal, border, and ischemic zones of the myocardium and also determination of the conditions in which isoproterenol either improves or impairs function in these zones, in the presence of obstruction to flow through one major coronary vessel.

METHODS

23 dogs, weighing between 25 and 35 kg, were anesthetized with i.v. sodium pentobarbital, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, miniature pressure gauges[2] were implanted within the LV through a stab wound in the apex, and Doppler ultrasonic flow transducers were placed around either the left anterior descending or circumflex coronary arteries, 2–3 cm from the bifurcation of these vessels. Hydraulic occluders were implanted just distal to the flow transducers and heparin-filled Tygon[3] catheters were implanted in the left atrium. In 6 of these dogs, ultrasonic diameter transducers[4] were implanted on opposing endocardial surfaces of the LV, while in the other 17 dogs, up to 5 pairs of miniature ultrasonic transducers[4] were implanted intramyocardially, parallel to the muscle fibers, 1–2 cm apart and varying in depth from 3 to 12 mm, in normal, border, and ischemic zones.

The miniature pressure gauges[5] were calibrated in vitro and in vivo against a calibrated Statham P23 Db strain gauge manometer.[5] Diastolic pressure was calibrated with left atrial diastolic pressure as a reference. At autopsy the position of the gauges within the ventricular cavity was confirmed. Coronary blood flow was measured with an ultrasonic Doppler flowmeter (5, 6).

An improved ultrasonic transit-time dimension gauge was used to measure LV diameter (D) (7); it measures the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5×10^6 mm/s between the 3-MHz piezoelectric crystals sutured to the LV endocardium at opposing sites. It was calibrated by substituting signals of known time duration from a calibrated, crystal-controlled pulse generator. A voltage proportional to transit time was recorded and calibrated in terms of crystal separation. In this manner, a measure of the internal diameter of the LV was continuously recorded. A modification of this instrument was used to measure myocardial segment lengths (SL) in the normal, border, and ischemic zones. The dimension gauge was modified along the lines of the one used by Theroux et al. (8) to provide simultaneous measurement of several segment lengths. At a constant room temperature, the drift of the instrument due to the electronics is minimal, i.e., less than 0.01 mm in 6 h, and the frequency response is flat to 60 Hz. Any drift in the measuring system, i.e., in the instrument electronics, the data tape recorder, and the oscillograph that displayed data, were eliminated during the experiment by periodic calibrations. This involved substitution of pulses of precisely known duration from a crystal-controlled pulse generator having a basic stability of 0.001%. The outstanding feature of this measurement technique is its overall stability. Additionally, the measurement technique does not rely on individual transducer calibration for gain and relative field strength, as does the electromagnetic induction method. The instrument used in the present study was modified further to provide simultaneous measurement of five segments and the regional electrograms from the intramyocardial ultrasonic transducers (Fig. 1). Thus, the instrument provided capability for simultaneous measurement of mechanical function in terms of SL and velocity (V) of myocardial fiber shortening and electrophysiological function in terms of ST segment elevation from up to five myocardial segments placed in normal, border, and ischemic zones. The position of the miniature ultrasonic transducers was confirmed at autopsy and minimal fibrosis, less than 1 mm, was observed at the site of implantation. Initially data were analyzed according to whether the transducers were subepicardial or subendocardial; since responses to coronary occlusion or to isoproterenol were similar for both transducer locations, the data were pooled for all intramyocardial transducers.

Regional myocardial blood flow was measured by the radioactive microsphere technique (9). The microspheres were ultrasonicated (Ultrasonic bath, model DA 0950)[6] for 5 min and mixed with a Vortex agitator.[6] Absence of microsphere aggregation was verified by microscopic examination. 1–2 million microspheres[7] (15±5 μm) labeled with ^{51}Cr, ^{85}Sr, or ^{141}Ce and suspended in 10% dextran, were injected through the catheter implanted in the left atrium for three determinations of blood flow; during control, then 10–15 min after coronary occlusion, and finally 5–20 min after isoproterenol infusion. A reference sample of arterial blood was withdrawn beginning 10 s before microsphere injection and continuing for 30 s after the injection was completed. After sacrifice of the animal, myocardial samples were weighed, placed in a gamma well counter,[8] and counted for 10 min. The raw counts were then corrected for background and cross-over and compared with the reference blood sample to obtain flow expressed in milliliters per minute per gram tissue, according to the formula:

Regional blood flow = (Counts per gram tissue/Counts per milliliter per minute reference blood).

Experiments were conducted 2–4 wk after operation. While the conscious, unsedated dogs rested quietly, control records of LV-diameter (D) and pressure (P), rate of change of diameter (dD/dt), i.e., the velocity of myocardial fiber shortening (V), the rate of change of pressure (dP/dt), coronary blood flow, arterial pressure, and heart rate were obtained in six dogs. In the other 17 dogs, instead of LVD and dD/dt, multiple segment lengths (SL) and velocity (V) of SL shortening were recorded, along with intramyocardial electrograms. After control measurements were recorded, including the first injection of microspheres, the coronary vessel was occluded and occlusion was confirmed by absence of coronary flow. Measurements were recorded continuously and the second microsphere injection was made 10–15 min after coronary occlusion. At 10–20 min after coronary occlusion, isoproterenol was infused at a rate of 0.4 μg/kg/min for 15 min to 3 h. The third microsphere injection was made 5–20 min after the beginning of isoproterenol infusion. In those 10 animals in which isoproterenol was infused for less than 30 min, final measurements were recorded 15–30

[2] Konigsberg P_{22}, Konigsberg Instruments, Inc., Pasadena, Calif.

[3] Norton Co., Plastics and Synthetics Div., Akron, Ohio.

[4] Construction details available from authors.

[5] Statham Instruments Div., Gould Inc., Oxnard, Calif.

[6] 3M Co., St. Paul, Minn.

[7] Scientific Industries, Inc., Queens Village, N. Y.

[8] Nuclear-Chicago, Searle Analytic, Inc., Lexington, Mass.

min after discontinuation of isoproterenol. Then, the animals were anesthetized with 30 mg/kg pentobarbital sodium, and sacrificed to confirm placement of intramyocardial transducers and to obtain myocardial samples at the same sites for regional blood flow determination.

Data were recorded on a multichannel tape recorder and played back on two multichannel direct-writing oscillographs at a paper speed of 100 mm/s. A cardiotachometer, triggered by the pressure pulse signal, provided instantaneous and continuous records of heart rate. Continuous records of dP/dt, dD/dt, and dSL/dt were derived from the signals of LVP, D, and SL, with Philbrick[9] operational amplifiers connected as differentiators having frequency responses of 60 Hz. A triangular wave signal with known slope (rate-of-change) was substituted for P, D, and SL signals to calibrate the differentiators directly.

The effects of interventions on myocardial contractility were assessed by measurements of the velocity of shortening and intraventricular pressure, peak dP/dt, and the quotient of dP/dt and developed pressure (left ventricular isovolumic minus end-diastolic pressure), i.e. (dP/dt/P). These techniques for evaluating the myocardial contractile state have been described in detail previously (1, 3, 10–12). The effects of interventions on regional myocardial function were assessed by measurement of stroke shortening, velocity of segment shortening, and end-diastolic and end-systolic segment lengths. End-diastolic segment length was the point just before isovolumetric contraction. End-systole coincided with isovolumetric relaxation. These points were readily identifiable in most instances. However, the precise timing of the end-systolic point may have varied by as much as 0.01 s, which could introduce a slight error in some ischemic segments.

Average and SEM values were calculated. The three states (control, occlusion, and occlusion plus isoproterenol) were compared in each animal by the paired t test (13).

RESULTS

While data were collected continuously, only those values during steady states in the control period, 10–15 min after coronary occlusion, and 5–30 min after the beginning of isoproterenol infusion are presented.

The results for myocardial segment function were grouped according to normal, border, moderately, and severely ischemic zones. The following three criteria were used to classify the segments: (*a*) anatomical placement determined at operation by a brief coronary occlusion resulting in an area of cyanosis: this was confirmed at autopsy when methylene blue dye was injected distal to the occlusion to determine areas of perfusion of that vessel; (*b*) ST segment elevation measured at the J point of the regional electrogram and averaged for the two sites between which function was measured; and (*c*) impairment of mechanical function, i.e., stroke SL shortening and velocity of SL shortening. Normal segments located at least 2–3 cm from the border of the cyanotic area showed neither significant ST elevation during occlusion nor reduction of function. Severely ischemic segments were in the central cyanotic area and showed ST elevation and complete loss of function, i.e., either they did not shorten during occlusion or showed systolic expansion. Specifically, complete loss of function is defined as the point where end-systolic SL equals end-diastolic SL and velocity is zero. When end-systolic SL was greater than end-diastolic SL, expansion during systole was considered to have occurred, i.e. paradoxical pulsation. Since velocity of SL shortening in the presence of paradoxical motion has little meaning, it was considered zero by definition. Moderately ischemic segments had reduced mechanical function by over 30% from control and average ST segment elevation (> 5 mV) in the two sites during occlusion. Border zone segments had reduced function of less than 25% from control and ST segment elevation (< 4 mV) during occlusion.

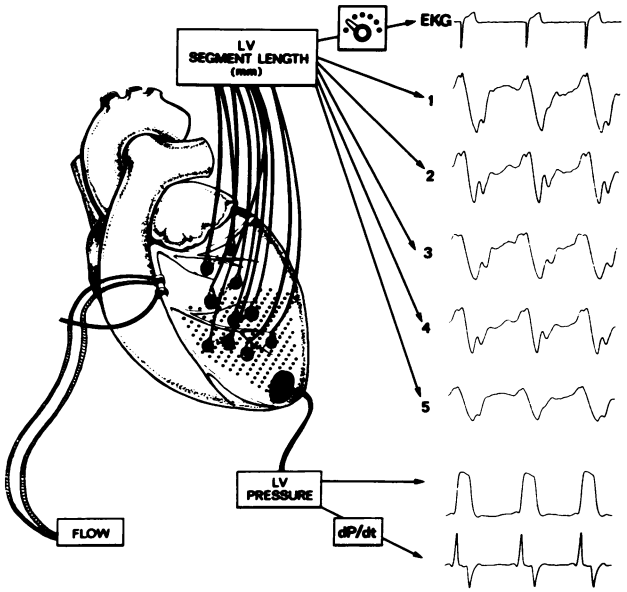

FIGURE 1 The techniques used to correlate regional myocardial function and electrograms in the conscious dog are shown schematically. A hydraulic occluder and coronary flow probe are implanted on either the left circumflex artery or, as in this illustration, the left anterior descending coronary artery. The measurement of absence of coronary flow confirms complete occlusion. A miniature pressure gauge is implanted in the left ventricle for pressure and dP/dt. Up to five pairs of miniature ultrasonic crystals are implanted intramyocardially for the measurement of segment length, velocity, and electrograms in normal, border, and ischemic zones.

The magnitude of SL shortening and velocity depend, in part, upon the size of the SL sample. Since this value was nearly identical for the four zones studied (Table I), changes from control in absolute numbers were compared.

Overall LV function (six dogs)

Coronary occlusion. Heart rate rose from 75±4 to 95±4 beats/min ($P < 0.01$). Systolic LV pressure, peak

[9] Teledyne Philbrick Co., Dedham, Mass.

TABLE I

The Effects of Coronary Occlusion and of Isoproterenol on Regional Zones

	Normal zone	Border zone	Moderately ischemic zone	Severely ischemic zone
End-diastolic SL, *mm*				
Control	14.26±1.02	13.84±0.61	14.13±0.85	14.13±0.48
Occlusion	14.37±1.01*	14.08±0.61*	14.57±0.93*	14.60±0.47*
Occl & iso	13.96±0.95*§	13.72±0.58‡§	14.29±0.89§	14.08±0.46§
End-systolic SL, *mm*				
Control	12.72±0.92	12.34±0.54	12.47±0.69	12.52±0.37
Occlusion	12.78±0.92	12.79±0.56*	13.97±0.94*	14.80±0.47*
Occl & iso	12.02±0.87*§	11.86±0.52§	12.94±0.86*§	14.77±0.47*
Stroke SL, *mm*				
Control	1.54±0.14	1.49±0.11	1.73±0.23	1.62±0.14
Occlusion	1.58±0.13	1.29±0.11*	0.60±0.08*	−0.20±0.04*
Occl & Iso	1.93±0.12*§	1.86±0.14*§	1.36±0.20*§	−0.69±0.09*§
Velocity SL, *mm*				
Control	16.7±1.1	18.8±1.2	19.6±2.4	18.3±0.8
Occlusion	16.6±1.1	16.0±1.0*	8.5±1.0*	0*
Occl & iso	33.1±2.6*§	29.4±2.2*§	19.1±2.4§	0*
ST segment, *mV*				
Control	0.2±0.1	0.2±0.1	0.2±0.1	0.2±0.1
Occlusion	0.3±0.1	1.3±0.2*	8.9±0.5*	11.4±1.3*
Occl & iso	0.7±0.2	4.7±0.6*§	11.1±0.6*§	15.3±1.7*§
Myocardial blood flows, *ml/min/g*				
Control	0.86±0.10	0.83±0.06	0.88±0.11	0.80±0.04
Occl	0.96±0.12	0.76±0.07‡	0.59±0.05*	0.20±0.03*
Occl & iso	1.88±0.29*§	1.37±0.12*§	1.13±0.16*§	0.21±0.05*

* Significantly different from control value, $P < 0.01$.
‡ Significantly different from control value, $P < 0.05$.
§ Significantly different from occlusion value, $P < 0.01$.
‖ Significantly different from occlusion value, $P < 0.05$.

dP/dt, and dP/dt/P showed initial transient reductions but were not significantly different from control at 10–15 min after occlusion. LV end-diastolic and systolic diameters and end-diastolic pressure rose slightly ($P < 0.01$) (Table II). These responses were similar for both left anterior descending and circumflex occlusions.

Isoproterenol. During the steady state, heart rate, peak dP/dt, and dP/dt/P doubled, while V rose from

TABLE II

Effects of Isoproterenol on Overall LV

	Control	Occlusion	Occlusion and isoproterenol
Heart rate, *beats/min*	75 ±4	95±4*	171±9*‡
LV end-diastolic diameter, *mm*	35.1±0.7	36.6±0.8*	34.4±0.6‡
LV end-systolic diameter, *mm*	25.7±0.7	27.6±0.8*	25.1±0.8*‡
LV pressure: (Peak systolic/end diastolic), *mm Hg*	123±3 / 8±1	123±3 / 10±1*	125±5 / 6±1*‡
Peak velocity, *mm/s*	75±3	71±5	107±13*‡
Peak dP/dt, *mm Hg/s*	3,330±170	3,180±140	6,050±300*‡
dP/dt/P, s^{-1}	57±4	54±4	103±4*‡

* Significant change from control, $P < 0.01$.
‡ Significant change from occlusion, $P < 0.01$.

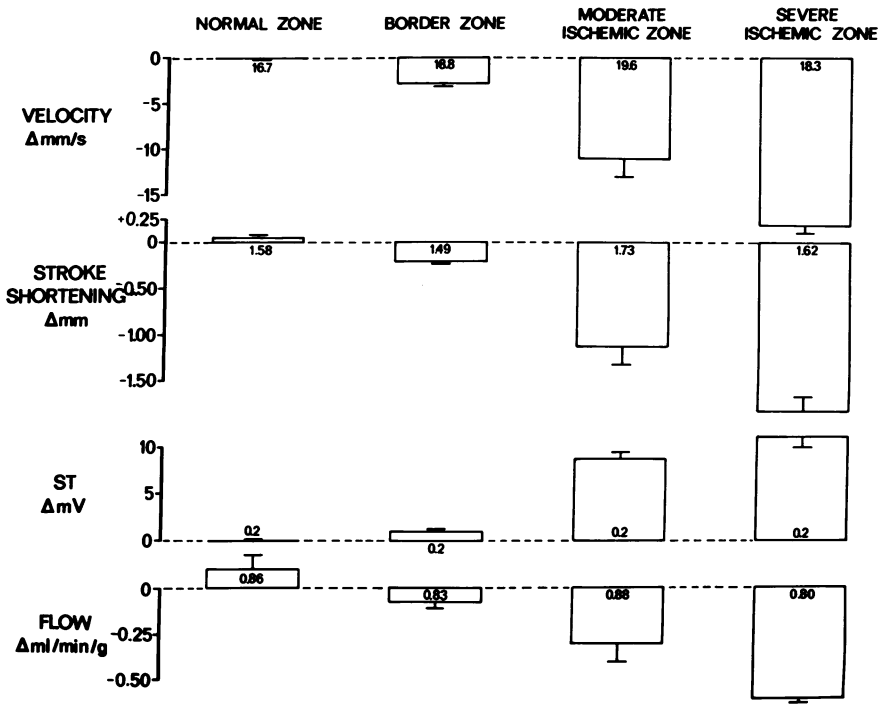

FIGURE 2 The effects of coronary occlusion on regional function, ST segment elevation, and blood flow, expressed as change from control. The preocclusion control values are noted at the base of the bars. With coronary occlusion, progressively greater impairment of function occurred, along with greater ST segment elevation and reduction in coronary blood flow in the four zones studied.

71±5 to 107±13 mm/s. Significant reductions ($P <$ 0.01) were observed in LV end-diastolic pressure (4 ±1 mm Hg), LV end-diastolic diameter (2.2±0.4 mm), and LV end-systolic diameter (2.5±0.5 mm). By 30 min after discontinuation of isoproterenol, all measurements had returned to preinfusion values.

Normal zone (17 segments in 17 dogs) (Table I)

Coronary occlusion. No significant changes in regional function, ST segment elevation, or regional blood flow were observed (Fig. 2).

Isoproterenol (Fig. 3). End-systolic SL fell more than end-diastolic SL, resulting in an increase in SL shortening of 0.35±0.04 mm, while V rose by 16.7±1.6 mm/s. Coronary flow rose by 0.90±0.21 ml/g per min. All changes were significant ($P < 0.01$) except for the ST segment potential, which did not change. By 30 min after discontinuation of isoproterenol, mechanical function had returned to preinfusion levels.

Isoproterenol (3-h infusion). When isoproterenol infusion was sustained for 3 h, function in the normal zone remained enhanced by essentially the same amounts reported in the paragraph above.

Border zone (21 segments in 17 dogs) (Table I)

Coronary occlusion (Fig. 2). End-diastolic SL rose less than end-systolic SL, resulting in a reduction in SL shortening of 0.20±0.03 mm, while V fell by 2.8±0.6 mm/s. The ST segments were elevated by 1.1±0.2 mV. All changes were significant ($P < 0.01$). Coronary flow fell by 0.07±0.03 ml/min per g ($P < 0.05$).

Isoproterenol (Fig. 3). In 19 of 21 segments, isoproterenol improved function substantially; end-systolic SL decreased more than end-diastolic SL, resulting in an increase in SL shortening of 0.57±0.06 mm, while V rose by 13.4±1.4 mm/s. ST segment elevation increased by 3.6±0.9 mV. Coronary flow rose by 0.62 ±0.10 ml/min per g. All changes were significant ($P < 0.05$). By 30 min after discontinuation of isoproterenol, values for mechanical function and ST elevation were not significantly different from preinfusion values in those experiments in which isoproterenol was infused for less than 30 min. When isoproterenol was infused longer, recovery values were not recorded.

In the other two border segments studied, function deteriorated within the first few minutes of isoproterenol infusion; end-systolic SL rose more than end-diastolic

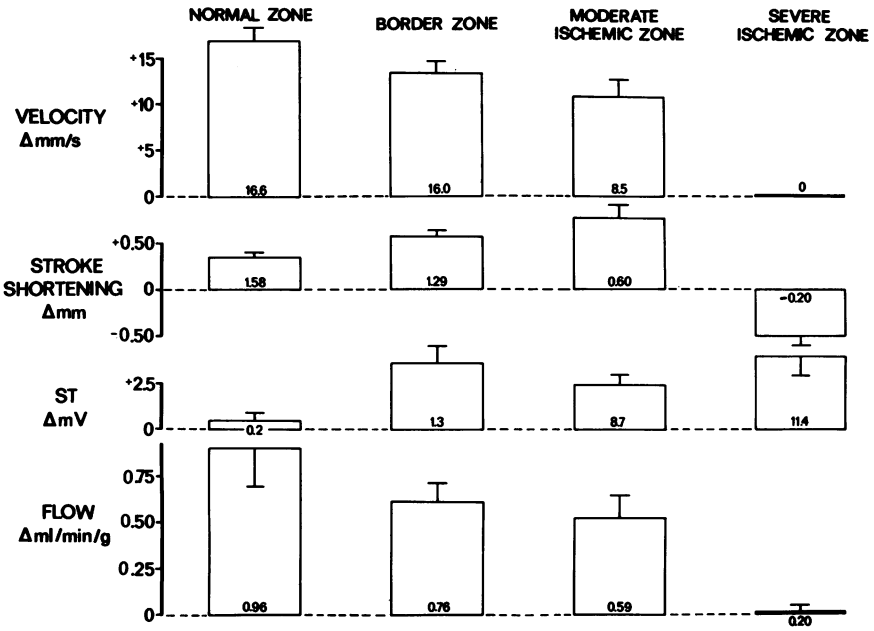

FIGURE 3 The effects of isoproterenol, 0.4 μg/kg/min, in the presence of coronary occlusion on regional function, ST segment elevation, and blood flow, expressed as change from control. The preisoproterenol control values are noted at the base of the bars.

SL, and systolic expansion was observed as V and systolic SL shortening fell to 0 (Fig. 4). ST elevation rose in both segments by an average of 6 mV and coronary flow fell in both by an average of 0.58 ml/min. Upon discontinuation of isoproterenol, infused for 15 min, function returned only partially in these two segments. This was in contrast to the results in those segments that showed improvement with isoproterenol, where function returned to the preisoproterenol level.

Isoproterenol (3-h infusion). From the steady state point at which data were presented in the preceding section, little further change in function was observed (Fig. 5); end-diastolic SL fell by 0.06±0.05 mm, end-systolic SL fell by 0.09±0.04 mm, stroke shortening rose by 0.03±0.01 mm, and velocity rose by 2.7±0.9 mm/s. These changes were not statistically significant.

Moderately ischemic zone (17 segments in 17 dogs) (Table II)

Coronary occlusion (Fig. 2). End-systolic SL rose more than end-diastolic SL, resulting in a reduction in SL shortening of 1.13±0.22 mm. ST segment elevation rose by 8.7±0.5 mV. Coronary flow fell by 0.29±0.05 ml/min per g.

Isoproterenol (Fig. 3). The reduction in end-systolic SL was greater than that of end-diastolic SL, resulting in an increase in SL shortening of 0.77±0.16 mm, while V rose by 10.7±1.9 mm/s (Fig. 6). ST segment elevation rose further, by 2.4±0.5 mV, and myocardial blood flow rose by 0.53±0.13 ml/min per g. All of these changes were significant ($P < 0.01$), but not significantly different from those observed in the border zone. By 30 min after discontinuation of isoproterenol, values for mechanical function and ST electrogram were not significantly different from preinfusion levels when isoproterenol was infused for less than 30 min. When isoproterenol was infused for more than 30 min, recovery values were not recorded.

Isoproterenol (3-h infusion). From the steady state point at which data were presented in the preceding section, little further change in function was observed; end-diastolic SL fell by 0.04±0.02 mm, end-systolic SL fell by 0.08±0.04 mm, stroke shortening rose by 0.04 ±0.02 mm, and velocity rose by 1.7±0.7 mm/s. These changes were not statistically significant.

Severely ischemic zone (25 segments in 17 dogs) (Table I)

Coronary occlusion (Fig. 2). In five of these segments, end-diastolic SL rose to a value identical to end-systolic SL, i.e. stroke SL shortening and V were 0. In the other 20 segments, end-systolic SL rose to a value even greater than end-diastolic SL, i.e., systolic expansion (paradoxical pulsation) occurred (Fig. 7). By definition, V fell to 0. ST segment elevation increased by 11.2±1.2 mV and myocardial blood flow fell by 0.60 ±0.04 ml/min per g. All changes were significant ($P < 0.01$).

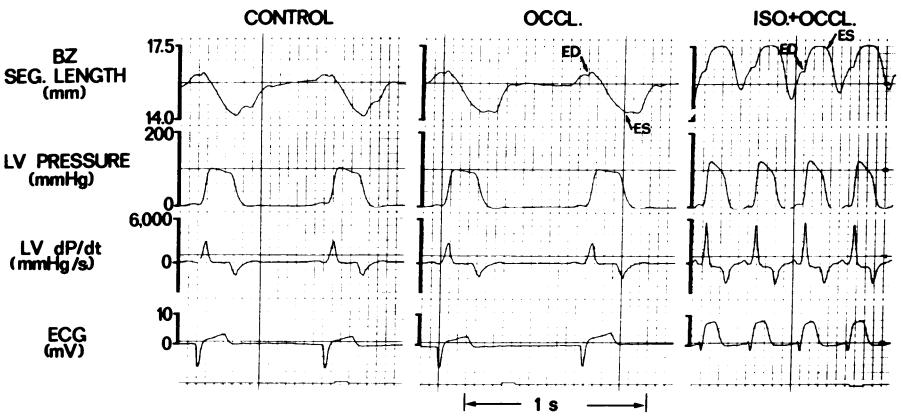

FIGURE 4 1 of 2 segments that responded to isoproterenol unlike the other 19 in the border zone. The phasic waveforms for segment length in the border zone (BZ) are shown along with LV pressure, dP/dt, and a regional electrogram from the BZ during control (left panel), after occlusion (middle panel), and with subsequent isoproterenol infusion (right panel). Occlusion impaired function minimally, while subsequent isoproterenol caused a drastic reduction in function, resulting in paradoxical motion, i.e., end-systolic (ES) SL was greater than end-diastolic (ED) SL.

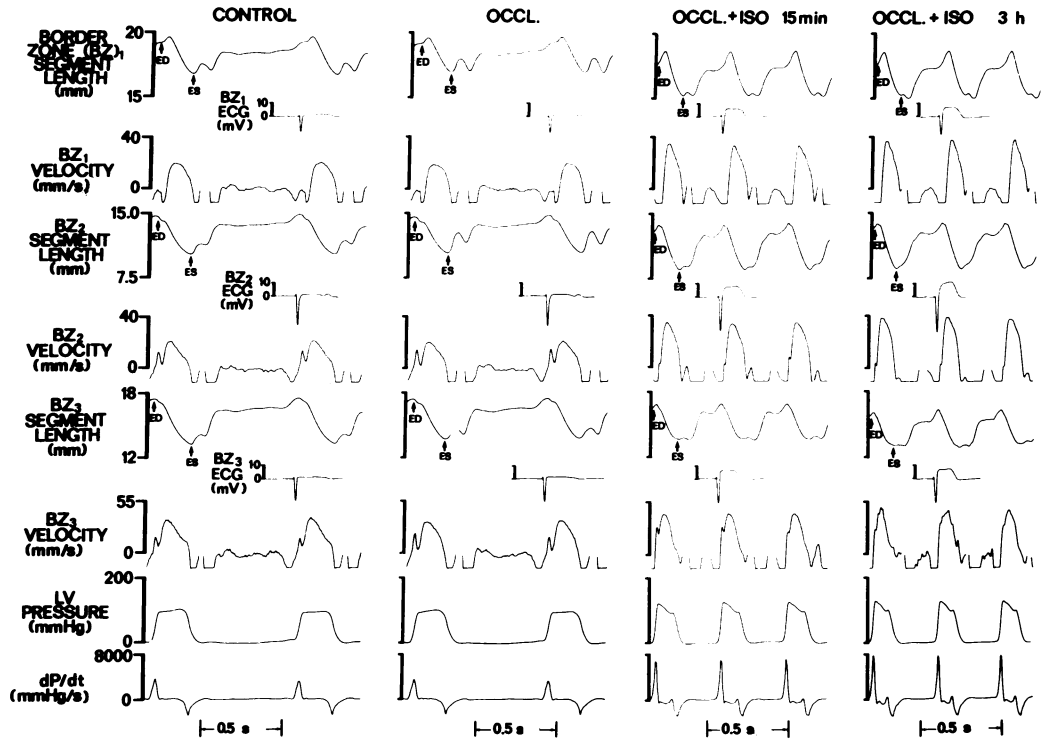

FIGURE 5 Phasic waveforms for segment length, velocity, and electrogram (ECG) for three border zones (BZ) from one animal are shown along with LV pressure and dP/dt during the control period, after 10 min of coronary occlusion (OCCL.), after 10 min of isoproterenol infusion (ISO), and finally after 3 h of isoproterenol infusion. Coronary occlusion induced only trivial impairment of regional function and elevation of ST in these three border-zone segments. Isoproterenol then improved function while establishing significant ST segment elevation in the regional electrograms. Maintenance of isoproterenol infusion for 3 h caused little further change. End-diastolic (ED) and end-systolic (ES) points are noted on selected segment length waveforms.

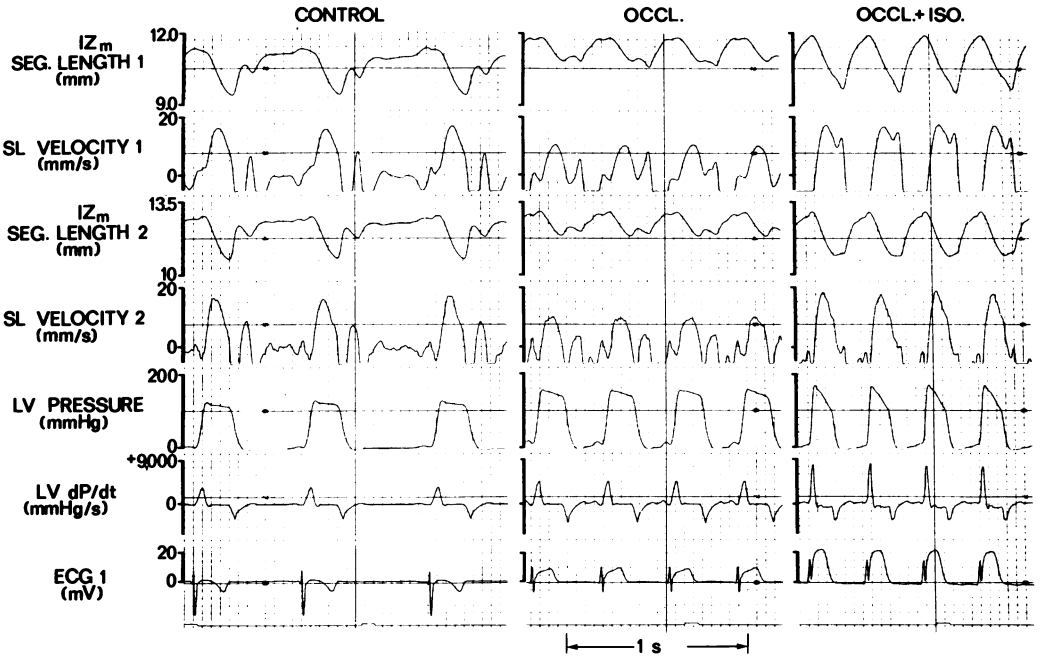

FIGURE 6 Phasic waveforms for segment length and velocity for two segments in the moderately ischemic zone (IZ_m) are shown, along with LV pressure, dP/dt, and an electrogram (ECG) from the first segment. Occlusion (center panel) impaired function substantially, which was then improved by isoproterenol.

Isoproterenol (*Fig. 3*). The five segments that did not shorten during systole exhibited systolic expansion after isoproterenol. In the other 20 segments, the paradoxical motion, already present, was intensified (Fig. 7). Thus, the paradoxical difference between end-systolic and end-diastolic SL actually rose during systole and was accompanied by further ST segment elevation of 3.9±0.9 mV. These changes were significant ($P < 0.01$). Myocardial blood flow did not change significantly with isoproterenol.

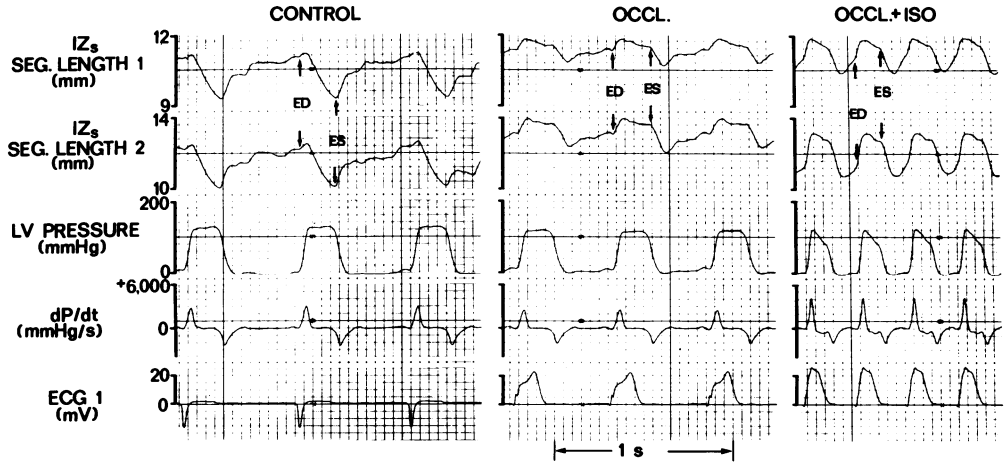

FIGURE 7 Phasic waveforms for two segments in the severely ischemic zone (IZ_s) are shown along with LV pressure, dP/dt, and regional electrogram from the first segment. Occlusion (middle panel) caused complete loss of function in these two segments. Even though shortening occurred during ejection, end-systolic (ES) size was greater than end-diastolic (ED) size in both instances, reflecting paradoxical motion. The paradoxical motion intensified with isoproterenol (right panel).

By 30 min after discontinuation of isoproterenol in those experiments in which isoproterenol was administered for less than 30 min, measurements of function returned almost to preinfusion levels. When isoproterenol was infused for more than 30 min, recovery values were not recorded.

Isoproterenol (3-h infusion). From the steady state point at which data were presented in the preceding paragraph, little further change in function was observed; all severely ischemic segments still functioned paradoxically, with end-systolic size greater than end-diastolic size.

DISCUSSION

Isoproterenol's potent positive inotropic action is well recognized. Because of this effect, along with its β_2 effect to dilate peripheral vessels, the drug became a popular mode of therapy for patients with a variety of low output states. Almost 10 yr ago, Elliott and Gorlin noted that myocardial function did not necessarily improve when isoproterenol was administered to patients with coronary artery disease (14), and Gunnar et al. observed that the clinical status of patients with cardiogenic shock could deteriorate with the drug (15). Mueller et al. observed that either myocardial lactate increased or extraction shifted to production with isoproterenol in patients with myocardial infarction (16). Maroko et al. showed that isoproterenol's strong chronotropic and inotropic actions, along with its hypotensive effect, resulted in augmentation of experimental infarct size in open-chest, anesthetized dogs (17). Because of these observations, administration of isoproterenol to patients with coronary occlusion has diminished.

In a previous study from this laboratory, the effects of isoproterenol were examined in conscious dogs in the presence and absence of marginal, global myocardial ischemia, induced by partial constriction of the left main coronary artery (1). Under these two circumstances, opposing reactions to the drug were observed. Although in the normal heart, the drug induced a marked improvement in function, in the presence of global ischemia, it improved function only transiently and then produced a paradoxical deterioration in cardiac performance, resulting in acute cardiac failure. It was postulated that the increases in cardiac rate and contractility elevated myocardial oxygen demands, which were not met by appropriate increases in oxygen supply, i.e., coronary flow. The marked disparity between oxygen demand and supply resulted in acute cardiac failure.

Thus, the response to isoproterenol is clear in these two extreme situations, one in which coronary perfusion is normal and the other in which coronary perfusion is fixed to the entire ventricle. However, myocardial ischemia is generally not an all-or-none phenomenon, but is frequently limited to only one portion of the ventricle; the ventricle may be normal in another part, while intermediate zones depend, to a great extent, upon availability of collateral blood flow. To simulate this situation of regional ischemia, only one major coronary artery was occluded in the present study. Under these conditions, isoproterenol infusion improved overall cardiac performance, as measured by LV diameter, pressure, velocity, and dP/dt/P, to a degree intermediate between what was previously observed in normal, conscious dogs in the presence and absence of global myocardial ischemia (1). These techniques, however, do not accurately reflect the responses of the different zones of myocardium in the presence of regional ischemia. Accordingly, regional measurements were made in the present study in four zones: normal, border, moderately ischemic, and severely ischemic. As could be predicted, responses of the four zones differed markedly in response to coronary occlusion and to the subsequent isoproterenol administration.

The severely ischemic zone was characterized by the greatest reduction in coronary flow, the greatest ST segment elevation, and absence of shortening during systole. In fact, 80% of these segments exhibited paradoxical motion during systole. Function deteriorated with isoproterenol in all segments measured; either systolic expansion developed in segments that did not shorten during systole, or the extent of paradoxical bulging increased. This was associated with further ST segment elevation, as has been reported previously (17). Coronary flow did not change significantly in these segments with isoproterenol. Thus, the increased myocardial oxygen demand was not met by an appropriate increase in flow, resulting in an intensification of ischemia reflected by further ST segment elevation and appearance or augmentation of paradoxical motion.

In contrast to the deterioration of function in severely ischemic myocardium, segments in moderately ischemic zones uniformly exhibited improved regional blood flow and function with isoproterenol, despite significant initial and further elevation of the ST segment. At first, it was hypothesized that the improvement in function was temporary and that the elevated ST segments were a harbinger of imminent deterioration. This was not the case. Even the infusion of a relatively large dose of isoproterenol, 0.4 μg/kg per min for up to 3 h, failed to reverse the salutary effects on regional myocardial function (Fig. 5). It could be, however, that with even longer isoproterenol infusions, e.g., for 24 h, deterioration in function might have occurred. It is also possible that the myocardial segment measured contained two populations of cells: those destined for salvage and those destined for necrosis. If this were the case, then the number of cells destined for necrosis may have increased, thereby causing further elevation of the ST segment, while sparing sufficient myocardium to main-

tain and even enhance function in that segment. Regardless of the explanation, it is important to emphasize that the status of regional myocardial function could not, in this case, be predicted from the electrophysiological event; in fact a dissociation occurred between the effects of isoproterenol on myocardial function and on the current of injury, as observed previously in this laboratory during recovery from brief coronary occlusions (12).

In general, the border zone behaved like the moderately ischemic zone, in that mechanical function improved along with regional blood flow while ST segment elevation either increased or appeared *de novo*. Conversely, with discontinuation of isoproterenol, mechanical and electrophysiological function returned to the preinfusion levels, suggesting that no permanent damage had been caused by the inotropic intervention. Those segments in the border and moderately ischemic zones in which function improved with isoproterenol received more blood flow in approximately the same proportion as that delivered to the normal zone. Thus, when flow can increase to marginally ischemic myocardium, apparently through collateral channels, but possibly through interdigitation of primary vessels originating from the unoccluded coronary artery, function can be maintained or enhanced with a strong inotropic agent such as isoproterenol (Figs. 5, 6). A recent study by Kerber et al. (18), conducted in open-chest, anesthetized dogs, also found that isoproterenol generally improved function. It is interesting that Kerber et al. observed both increased early-systolic aneurysmal bulging and then improved posterior wall motion with isoproterenol (18). Since an echocardiograph device was used in that study to assess posterior wall motion, it is possible that myocardial segments, 1–2 cm apart anatomically, could not be differentiated functionally, but their effects might be summed. If so, then it is understandable how the study by Kerber et al. (18) reported both increased bulging, observed in the severely ischemic zone in the present study, and improved wall motion, observed in the adjacent, moderately ischemic, and border zones in the present study.

There were 2 border-zone segments of the 21 examined in the present study that deserve special attention, in that function deteriorated strikingly with isoproterenol (Fig. 4). With coronary occlusion, these segments functioned well enough and exhibited sufficiently little ST segment elevation to be classified in the border zone. Yet with isoproterenol, function deteriorated rapidly and paradoxical motion was observed. It is interesting to note that in both of these segments, blood flow fell sharply with isoproterenol, suggesting that a "steal" may have occurred and might have been in part responsible for the deterioration in function.

In conclusion, in the conscious dog with regional myocardial ischemia induced by complete occlusion of one major coronary vessel, isoproterenol can elicit a spectrum of reactions in tissues of varying ischemia. Myocardial function deteriorated with isoproterenol in severely ischemic zones, whereas almost all segments in moderately ischemic and border zones as well as in the normal zone showed improved function, in the face of augmented ST segment elevation. In contrast to the majority of data, function was completely lost in two border-zone segments during isoproterenol infusion. The results for mechanical function correlated well with regional flow determinations, which indicated enhanced perfusion along with improved function on the one hand, and a reduction in perfusion in those two segments that behaved paradoxically on the other. Where coronary perfusion to the myocardium is fixed and cannot increase, as in experiments with global myocardial ischemia (1), increases in myocardial oxygen demand induced by isoproterenol were not met by an increase in oxygen delivery. Accordingly, the myocardium rapidly outstripped its nutrient supply with resultant deterioration in performance. Since the extent of coronary artery disease and collateral circulation varies in patients with myocardial infarction, and also since the canine model is not directly applicable to the human, it is difficult to provide a simple statement on the use of isoproterenol in the clinical setting. In general, the clinical extrapolation of these results suggests that isoproterenol can improve function when only one portion of the myocardium is ischemic, depending upon availability of collateral channels, and perhaps at the expense of intensification of ischemia.

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