# Effects of Propranolol on Regional Myocardial Function, Electrograms, and Blood Flow in Conscious Dogs with Myocardial Ischemia

STEPHEN F. VATNER, HANK BAIG, W. THOMAS MANDERS, HERMANN OCHS, and MASSIMO PAGANI

*From the Departments of Medicine, Harvard Medical School and Peter Bent Brigham Hospital, the Department of Cardiology, Children's Hospital Medical Center, Boston, Massachusetts 02115 and the New England Regional Primate Research Center, Southboro, Massachusetts 01772*

ABSTRACT The effects of coronary occlusion and of subsequent propranolol administration were examined in 18 conscious dogs. Overall left ventricular (LV) function was assessed by measurements of LV pressure and dP/dt, and regional myocardial function was assessed by measurements of segment length (SL), velocity of SL shortening and regional myocardial "work", i.e., pressure-length loops in normal, moderately, and severely ischemic zones. Regional intramyocardial electrograms were measured from the same sites along with regional myocardial blood flow as determined by the radioactive microsphere technique. Coronary occlusion resulted in graded loss of function from the normal to severely ischemic zones with graded flow reduction and graded elevation of the ST segment. Propranolol depressed overall LV function, function in the normal zone (work fell by 17±4%), and in the majority of moderately ischemic segments (work fell by 7±3%). In severely ischemic segments the extent of paradoxical motion and post-systolic shortening was reduced by propranolol. After propranolol regional myocardial blood flow fell in the normal zone (11±2%) and rose in the moderately (15±4%) and severely (63±10%) ischemic zones. Thus, in the conscious dog with regional myocardial ischemia, propranolol induces a redistribution of myocardial blood flow, with flow falling in normal zones and rising in moderately and severely ischemic zones. The improvement in perfusion of ischemic tissue was associated with slight but significant depression of shortening, velocity, and work in the moderately ischemic zones and of paradoxical bulging and post-systolic shortening in the severely ischemic zone.

## INTRODUCTION

Propranolol has been shown to reduce experimental infarct size after coronary occlusion in anesthetized animal preparations (1–3). Two possible mechanisms, which would result in protection of ischemic myocardium, involve an increase oxygen supply, i.e., in blood flow, or a reduction in oxygen demands, i.e., the work of the ischemic tissue. Prior studies in anesthetized animals have consistently shown no effect of propranolol on blood flow to ischemic myocardium (4–6), while previous studies on the effects of beta adrenergic blockers on function of ischemic tissue have been controversial. On the one hand propranolol has been shown to depress overall left ventricular function (7–9) and regional function (10) of the ischemic heart, while on the other hand beta adrenergic blockers have also been shown to improve regional function in the presence of ischemia (11, 12).

While prior studies have examined the effects of beta adrenergic blockers on measurements of electrograms (1–3, 5, 10, 13) mechanical function (10–12), and regional myocardial blood flow (4–6) in the ischemic heart, these measurements have not been correlated in the same study. Moreover, most of these previous studies have been conducted in anesthetized animals with an open chest (1–6, 10, 12, 13), where the myocardial depressant effects of the anesthesia (14, 15) and recent surgery could intensify the depressant effects of the beta adrenergic blocker. It is also important to keep in mind that in the presence of regional myocardial ischemia, measurements of overall function can be misleading, since function can be entirely normal in one portion of the heart and absent in another. Accordingly, this investigation

Dr. Vatner is an Established Investigator of the American Heart Association. Dr. Pagani is a Postdoctoral Research Fellow, 1 F05 TW02331-01, of the U. S. Public Health Service.

*Received for publication 31 December 1976 and in revised form 14 March 1977.*

was conducted in conscious dogs, in which the effects of propranolol were examined with simultaneous measurements of regional myocardial function, blood flow, and electrograms in normal, moderately, and severely ischemic zones. The specific goals of this study were to ascertain (*a*) whether function of ischemic myocardium improved or deteriorated with propranolol and (*b*) whether in the conscious dog, the change in function was associated with an alteration in blood flow to the ischemic myocardium.

## METHODS

30 dogs, weighing between 25 and 35 kg, were anesthetized with i.v. pentobarbital sodium, 30 mg/kg. Through a thoracotomy in the fifth left intercostal space, miniature pressure gauges ($P_{22}$, Konigsberg Instruments, Inc., Pasadena, Calif.) were implanted within the left ventricle through a stab wound in the apex, and Doppler ultrasonic flow transducers were placed around either the left anterior descending (18 dogs) or circumflex coronary arteries (12 dogs), 2–3 cm from the bifurcation of these vessels. Hydraulic occluders were implanted just distal to the flow transducers and heparin-filled Tygon catheters (Norton Co., Plastics & Synthetics Div., Akron, Ohio) were implanted in the left atrium and aorta. Up to six pairs of miniature ultrasonic transducers[1] were implanted intramyocardially, parallel to the muscle fibers, 1–2 cm apart and varying in depth from 4 to 15 mm, in potentially normal, moderately, and severely ischemic zones.

The miniature pressure gauges were calibrated in vitro and in vivo against a calibrated Statham P23 Db strain gauge manometer (Statham Instruments Div., Gould, Inc., Oxnard, Calif.) connected to the left atrial and aortic catheters. At autopsy the position of the gauges within the ventricular cavity was confirmed. Instantaneous coronary blood flow was measured with an ultrasonic Doppler flowmeter (16, 17). An improved ultrasonic transit-time dimension gauge was used to measure regional myocardial segment length (SL)[2] (11, 18, 19). The instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of approximately $1.5 \times 10^6$ mm/$\mu$s between the 3 MHz piezoelectric crystals, thus giving a record of instantaneous myocardial fiber length. At a constant room temperature the thermal drift of the instrument is minimal, i.e., less than 0.01 mm in 6 h. The frequency response is flat to 60 Hz. Any drifts 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 instrument used in the present study was modified further to provide simultaneous measurement of eight segment lengths and the regional electrogram from all crystal sites, located 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.

Regional myocardial blood flow was measured by the radioactive microsphere technique (20). The microspheres (3M Co., St. Paul, Minn.) were suspended in 0.01% Tween[80] solution (10% dextran) and placed in an ultrasonic bath for 60 min. They were subsequently agitated by direct application of an ultrasonic probe to insure dispersion of the spheres just before injection. Absence of microsphere aggregation was verified by microscopic examination. Before injection of microspheres, 0.7 ml of the Tween[80]—dextran solution (without microspheres) was injected to determine if the diluent for the microsphere suspension was to have an adverse effect on cardiac dynamics (21). Four to six million microspheres (9±2 $\mu$m) labeled with $^{46}$Sc, $^{51}$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 the onset of coronary occlusion, and finally 5–20 min after propranolol. A reference sample of arterial blood was withdrawn beginning 10 s before microsphere injection and continuing for 40 s after the injection was completed. After sacrifice of the animal, myocardial samples were obtained from the sites where function and electrograms were measured, dissected into epi- and endocardial layers, weighed, placed in a three-channel gamma well counter (Searle Analytic Inc., Des Plaines, Ill.), and counted in appropriately selected energy windows 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 of tissue.

Experiments were conducted 2–4 weeks after operation. While the conscious, unsedated dogs rested quietly, control records of left ventricular (LV) pressure (P), the rate of change of pressure (dP/dt), coronary blood flow, heart rate, 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 until termination of the animal. Measurements were recorded continuously and the second microsphere injection was made 10–15 min after coronary occlusion, at a time when measurements of regional myocardial function and electrograms were stable. At 15–20 min after coronary occlusion propranolol was injected in doses of 0.5 mg/kg (3 dogs), 1.0 mg/kg (12 dogs), and 2.0 mg/kg (3 dogs). Qualitative differences in response were not observed among the three doses. The third microsphere injection was made 5–20 min after propranolol. After 30 min of further recordings the animals were anesthetized with 30 mg/kg of pentobarbital sodium and sacrificed to confirm placement of intramyocardial transducers and to obtain myocardial samples at the same sites for regional blood flow determination. 12 additional dogs (controls) were studied with similar protocols. In the six control dogs studied for measurement of regional blood flow, saline instead of propranolol was administered before the third microsphere injection.

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, and dSL/dt were derived from the signals of LVP and SL with Philbrick (Teledyne Philbrick, Dedham, Mass.) operational amplifiers connected as differentiators having frequency responses of 700 and 140 Hz, respectively. A triangular wave signal with known slope (rate of change) was substituted for P and SL signals to calibrate the differentiators directly.

The effects of interventions on regional myocardial function were assessed by measurement of stroke shortening,

[1] Construction details available from the authors.

[2] *Abbreviations used in this paper*: dP/dt, rate of change of pressure; ENDO-EPI, endocardial/epicardial flow ratio; LV, left ventricular; P, pressure; SL, segment length; V, velocity.

velocity of segment shortening, and end-diastolic and end-systolic segment lengths. In addition an $x$-$y$ plot of the instantaneous LV pressure and regional SL signals were recorded and photographed from a storage oscilloscope. The area described by this loop was taken as an index of regional myocardial "work" in units of millimeters Hg–millimeter. End-diastolic 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 in each animal (control, occlusion, and occlusion plus propranolol) were compared by the paired $t$ test, while changes between states were compared in the untreated controls and propranolol-treated animals by the unpaired $t$ test (22).

## RESULTS

### *Effects of coronary occlusion*

#### Overall LV Function ($n$ = 18) (Table I)

After coronary occlusion, heart rate rose by 31±5%, $P < 0.01$, from a control of 81±4 beats/min. LV systolic pressure and peak dP/dt did not change significantly, from control levels of 114±2 mm Hg and 3,330±140 mm Hg/s, respectively.

#### Regional LV Function (Figs. 1, 2; Table II)

*Normal zone (19 segments).* After coronary occlusion end-diastolic SL, SL stroke shortening, velocity, and work did not change significantly.

Table I

*Overall LV Function: Effects of Coronary Occlusion and Subsequent Propranolol Administration ($n$ = 18) Compared with Untreated Controls ($n$ = 12)*

| | Preocclusion control | Occlusion | Occlusion and propranolol |
|---|---|---|---|
| LV systolic pressure, *mm Hg* | | | |
| Propranolol | 114±1.5 | 115±2.9 | 116±3.1 |
| Untreated | 114±2.4 | 118±3.1 | 117±3.2 |
| LV dP/dt, *mm Hg/s* | | | |
| Propranolol | 3,330±140 | 3,240±150 | 2,700±110*‡§ |
| Untreated | 3,130±150 | 3,090±150 | 3,030±110 |
| Heart rate, *beats/min* | | | |
| Propranolol | 81±4.4 | 104±5.1*¶ | 96±3.9*‡¶ |
| Untreated | 80±3.3 | 116±3.3* | 118±3.6 |

* Significantly different from preocclusion control, $P < 0.01$.
‡ Significantly different from occlusion value, $P < 0.01$.
§ Response of two groups significantly different, $P < 0.01$.
¶ Response of two groups significantly different, $P < 0.05$.

*Moderately ischemic zone (29 segments).* Coronary occlusion increased end-diastolic SL by 3.2±0.5% from a control of 17.6±1.0 mm and reduced SL stroke shortening by 59±4% from a control of 2.42±0.21 mm, velocity by 49±3% from a control of 24±2 mm/s, and work by 49±4%, from a control of 238±29 mm Hg–mm. All these changes were significant, $P < 0.01$.

*Severely ischemic zone (45 segments).* Coronary occlusion increased end-diastolic SL by 6.5±0.8%, from a control of 16.59±0.68 mm, and reduced stroke SL shortening by 116±4% from a control of 2.10±0.15 mm, velocity by 93±2% from a control of 23.3±1.7 mm/s, and "work" by 92±3% from a control of 229±19 mm Hg–mm. All these changes were significant, $P < 0.01$. Since the majority of these segments had larger end-systolic dimensions than end-diastolic dimensions (paradoxical motion), the reduction in SL stroke shortening was greater than 100%.

#### Intramyocardial Electrogram (Table III)

Coronary occlusion failed to elicit ST elevation in the normal zone, but increased ST elevation by 3.1 ±0.7 mV, $P < 0.01$, in the moderately ischemic zone

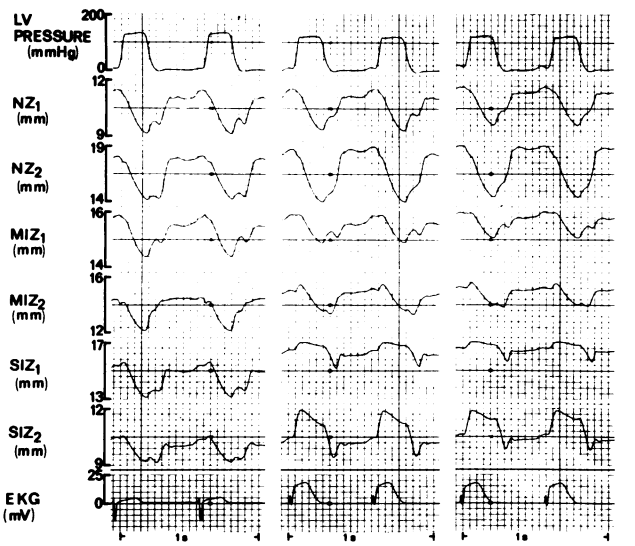


Figure 1 The simultaneous phasic wave forms at rapid paper speed are shown for left ventricular (LV) pressure, segment lengths in two normal zones (NZ), two moderately ischemic zones (MIZ), and two severely ischemic zones (SIZ), along with an electrogram from one of the severely ischemic segments during control (left panel), after coronary occlusion (middle panel), and after propranolol during coronary occlusion (right panel). With occlusion function fell slightly in one of the normal zones ($NZ_1$) and improved in the other ($NZ_2$). Function fell more strikingly in the moderately ischemic zones and was completely lost in the severely ischemic zones. Propranolol induced less dramatic effects, depressing function slightly in normal and moderately ischemic zones, and decreasing passive stretching in severely ischemic zones.

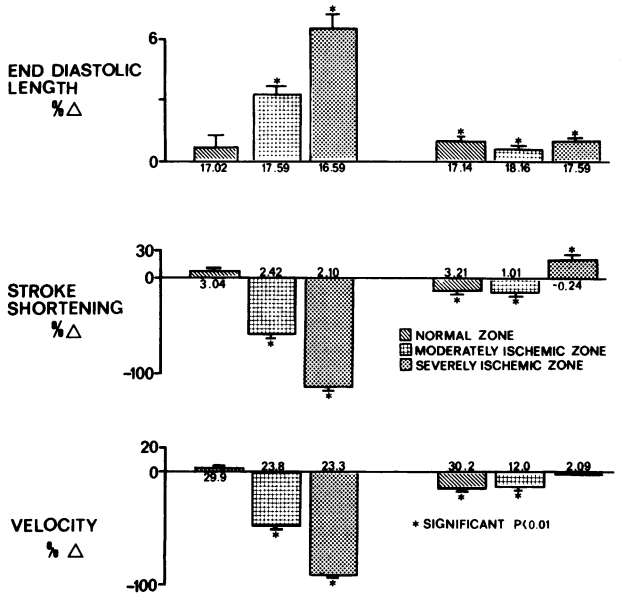


FIGURE 2 The effects of coronary occlusion (left panel) and of propranolol during occlusion (right panel) are shown as percentage change from control for end diastolic segment length, stroke shortening, and velocity of shortening for all segments in the normal, moderately ischemic, and severely ischemic zones. Significant changes from control are noted by the asterisks, while the average control values are noted at the base of the bars. While the effects of propranolol administration during coronary occlusion were generally statistically significant, they were small in relation to the effects induced by simple coronary occlusion.

and by 7.8±0.9 mV, $P < 0.01$ in the severely ischemic zone.

### REGIONAL MYOCARDIAL BLOOD FLOW (FIG. 3, TABLE IV)

With coronary occlusion flow did not change significantly from a control of 1.10±0.03 ml/min per g in the normal zone, but fell by 39±3%, $P < 0.01$, from a control of 0.92±0.03 ml/min per g in the moderately ischemic zone and by 82±2%, $P < 0.01$, from a control of 0.98±0.04 ml/min g in the severely ischemic zone (Fig. 3). The endocardial/epicardial (ENDO/EPI) flow ratio did not change significantly in the normal zone (control = 1.19±0.03) but fell ($P < 0.01$) in the moderately ischemic zone from 1.22±0.05 to 0.82±0.06, and from 1.19±0.03 to 0.63±0.08 in the severely ischemic zone.

## *Effects of propranolol in the presence of coronary occlusion*

### OVERALL LV FUNCTION (TABLE I)

Propranolol did not affect LV systolic pressure significantly, but reduced heart rate by 6.4±1.9%, $P < 0.01$,

TABLE II

*Regional Function: Effects of Coronary Occlusion and Subsequent Propranolol Administration (n = 18) Compared with Untreated Control Animals (n = 12)*

| | Preocclusion control | Occlusion | Occlusion and propranolol |
|---|---|---|---|
| Normal zone | | | |
| Stroke shortening, *mm* | | | |
| Propranolol | 3.04±0.25 | 3.21±0.27 | 2.79±0.26*‡¶ |
| Untreated | 1.88±0.29 | 2.04±0.27 | 2.02±0.27 |
| Velocity, *mm/s* | | | |
| Propranolol | 29.9±2.65 | 30.2±2.77 | 25.1±2.11*‡§ |
| Untreated | 23.1±2.83 | 23.8±2.26 | 23.7±2.22 |
| End diastolic length, *mm* | | | |
| Propranolol | 17.02±1.09 | 17.14±1.13 | 17.28±1.14*‡§ |
| Untreated | 16.95±1.82 | 17.18±1.86* | 17.15±1.88 |
| Moderately ischemic zone | | | |
| Stroke shortening, *mm* | | | |
| Propranolol | 2.42±0.21 | 1.01±0.12* | 0.92±0.13*‡§ |
| Untreated | 1.93±0.29 | 0.88±0.17* | 1.00±0.18* |
| Velocity, *mm/s* | | | |
| Propranolol | 23.8±1.67 | 12.0±0.91* | 11.0±1.02*‡§ |
| Untreated | 19.6±2.28 | 10.2±1.28* | 11.1±1.24* |
| End diastolic length, *mm* | | | |
| Propranolol | 17.59±0.99 | 18.16±1.03* | 18.47±1.06*‡¶ |
| Untreated | 13.85±1.08 | 14.24±1.18* | 14.21±1.18* |
| Severely ischemic zone | | | |
| Stroke shortening, *mm* | | | |
| Propranolol | 2.10±0.15 | −0.24±0.09* | −0.17±0.08*‡¶ |
| Untreated | 1.95±0.29 | −0.26±0.09* | −0.28±0.12* |
| Velocity, *mm/s* | | | |
| Propranolol | 23.3±1.69 | 2.09±0.80* | 1.74±0.76* |
| Untreated | 22.0±2.78 | 0.30±0.30* | 1.25±0.71* |
| End diastolic length, *mm* | | | |
| Propranolol | 16.59±0.68 | 17.59±0.70* | 17.77±0.71*‡§ |
| Untreated | 14.85±0.77 | 15.36±0.75* | 15.32±0.75* |

* Significantly different from preocclusion control, $P < 0.01$.
‡ Significantly different from occlusion value, $P < 0.01$.
§ Response of two groups significantly different, $P < 0.01$.
¶ Response of two groups significantly different, $P < 0.05$.

TABLE III

*Regional Electrocardiogram: Effects of Coronary Occlusion and Subsequent Propranolol Administration (n = 18) Compared with Untreated Controls (n = 10)*

| | Preocclusion control | Occlusion | Occlusion and propranolol |
|---|---|---|---|
| | | *mV* | |
| Normal zone | | | |
| Propranolol | 0.7±0.14 | 0.7±0.13 | 0.7±0.16 |
| Untreated | 0.8±0.25 | 0.6±0.27 | 0.7±0.29 |
| Moderately ischemic zone | | | |
| Propranolol | 0.9±0.12 | 4.0±0.71* | 3.9±0.72* |
| Untreated | 0.7±0.28 | 4.3±0.93* | 4.0±0.85* |
| Severely ischemic zone | | | |
| Propranolol | 0.6±0.09 | 8.5±0.93* | 8.7±0.91* |
| Untreated | 0.5±0.16 | 6.9±0.87* | 6.7±0.87* |

* Significant change from preocclusion control, $P < 0.01$.

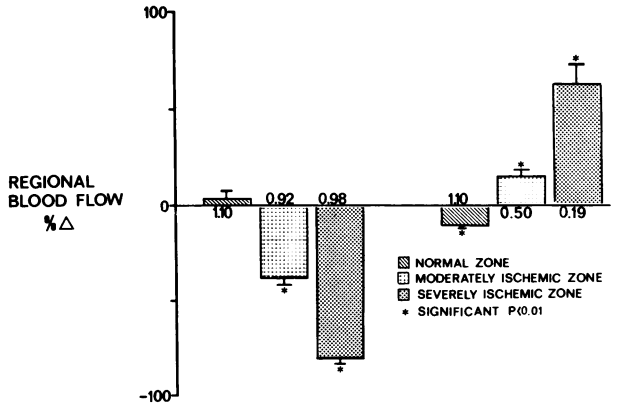


FIGURE 3 The effects of coronary occlusion (left) and subsequent propranolol during coronary occlusion (right) on regional myocardial blood flow are shown as percentage change from control for all segments studied in the normal, moderately ischemic, and severely ischemic zones. Significant changes from control are denoted by the asterisks while control values are noted at the base of the bars. Propranolol induced a significant redistribution of myocardial blood flow with flow falling in the normal zone and rising in the moderately and severely ischemic zones.

from an occlusion control of 104±5 beats/min and dP/dt by 15.4±2.1%, $P < 0.01$, from an occlusion control of 3,240±150 mm Hg/s.

## REGIONAL LV FUNCTION (FIGS. 1, 2, TABLE II)

*Normal zone.* Propranolol increased end-diastolic SL by 0.9±0.3%, $P < 0.01$, from an occlusion control of 17.1±1.1 mm, and reduced SL stroke shortening by 13.7±3.5%, $P < 0.01$, from an occlusion control of 3.21±0.27 mm, reduced velocity by 15±3%, $P < 0.01$, from an occlusion control of 30.2±2.8 mm/s, and reduced work by 17±4%, $P < 0.01$, (Fig. 4) from an occlusion control of 263±27 mm Hg–mm.

*Moderately ischemic zone.* Propranolol increased further end-diastolic SL by 0.58±0.18%, $P < 0.01$, from an occlusion control of 18.2±1.0 mm and reduced further SL stroke shortening by 17.2±5.3%, $P < 0.01$, and velocity by 13±4%, $P < 0.01$, from occlusion controls of 1.01±0.12 mm and 12.0±0.9 mm/s, respectively, and reduced work by 7±3%, $P < 0.05$ (Fig. 4), from an occlusion control of 118±15 mm Hg–mm. These figures represent the average values of 18 segments in which function fell, 5 segments in which function improved, and 5 segments in which function did not change. When the average changes in SL stroke shortening, velocity, and work were compared with those in the normal zone in terms of absolute numbers, as opposed to percent change, the decreases in these three parameters were less, $P < 0.01$, than observed for the normal zone.

*Severely ischemic zone.* Propranolol increased further end-diastolic SL by 0.99±0.21%, $P < 0.01$,

TABLE IV

*Regional Blood Flow and ENDO/EPI Ratios: Effects of Coronary Occlusion and Subsequent Propranolol Administration (n = 18) Compared with Untreated Controls (n = 5)*

| | Preocclusion control | Occlusion | Occlusion and propranolol |
|---|---|---|---|
| Flow, *ml/min/g* | | | |
| Normal zone | | | |
| Propranolol | 1.10±0.03 | 1.10±0.05 | 0.93±0.04*‡§ |
| Untreated | 1.31±0.06 | 1.50±0.10 | 1.48±0.09 |
| Moderately ischemic zone | | | |
| Propranolol | 0.92±0.03 | 0.50±0.03* | 0.58±0.04*‡§ |
| Untreated | 1.27±0.02 | 0.83±0.05* | 0.76±0.07* |
| Severely ischemic zone | | | |
| Propranolol | 0.98±0.04 | 0.19±0.01* | 0.26±0.02*‡§ |
| Untreated | 1.29±0.03 | 0.31±0.03* | 0.32±0.04* |
| ENDO/EPI Ratio | | | |
| Normal zone | | | |
| Propranolol | 1.19±0.03 | 1.22±0.03 | 1.28±0.03*‡ |
| Untreated | 1.20±0.04 | 1.24±0.04 | 1.28±0.05 |
| Moderately ischemic zone | | | |
| Propranolol | 1.22±0.05 | 0.82±0.06* | 0.89±0.07* |
| Untreated | 1.18±0.04 | 0.88±0.08* | 0.93±0.10 |
| Severely ischemic zone | | | |
| Propranolol | 1.19±0.03 | 0.63±0.08* | 0.64±0.07* |
| Untreated | 1.22±0.06 | 0.42±0.05* | 0.47±0.07* |

* Significantly different from preocclusion control, $P < 0.01$.
‡ Significantly different from occlusion value, $P < 0.01$.
§ Response of two groups significantly different, $P < 0.01$.

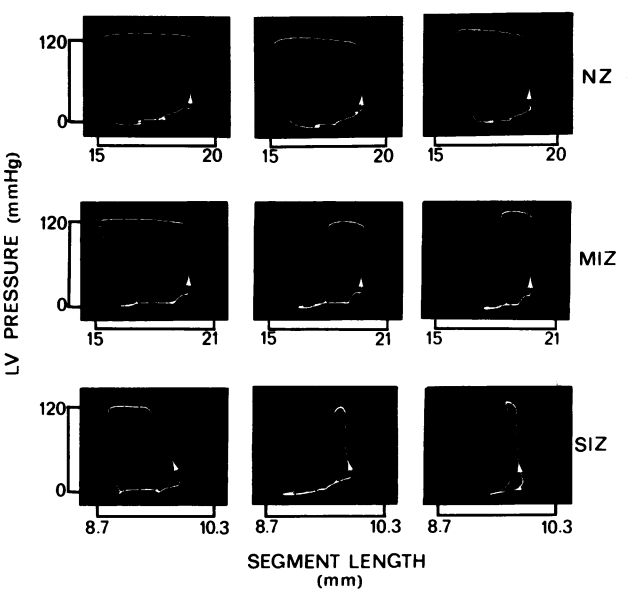


FIGURE 4 Left ventricular (LV) pressure-regional segment length loops, an index of regional myocardial work, are shown for a normal zone (NZ) (top), moderately ischemic zone (MIZ) (middle), and severely ischemic zone (SIZ) (bottom) during control (left panel) after coronary occlusion (middle panel) and after propranolol during coronary occlusion (right panel). Coronary occlusion induced progressively greater decreases in regional work in the three zones. With propranolol work fell further in all three zones. In addition the post-systolic shortening of the ischemic zone segment was reduced by propranolol administration.

from an occlusion control of 17.59±0.70 mm, and reduced paradoxical bulging in the severely ischemic segments, $P < 0.01$. However, function was never improved to the extent that a segment that bulged paradoxically began to shorten during ejection after propranolol administration. Work fell by 40±12%, $P < 0.01$, from an occlusion control of 40±8 mm Hg–mm in segments exhibiting positive work. One of the most prominent effects of propranolol was the reduction in post-systolic shortening in severely ischemic segments shown in the bottom, middle part of Fig. 4.

#### Intramyocardial Electrogram

Propranolol failed to lower ST elevation in the normal, moderately, or severely ischemic zones from the occlusion levels (Table III).

#### Regional Myocardial Blood Flow (Table IV)

Propranolol reduced flow in the normal zone by 11±2%, from an occlusion control of 1.10±0.05 ml/min per g and increased flows in the moderately (15 ±4%) and severely ischemic (63±10%) zones from occlusion controls of 0.50±0.03 and 0.19±0.01 ml/min per g, respectively (Fig. 3). These three changes in blood were significant, $P < 0.01$. Propranolol increased the ENDO/EPI ratio in the normal zone from 1.22±0.03 to 1.28±0.03, $P < 0.01$, and in the moderately ischemic zone from 0.82±0.06 to 0.89±0.07, $P < 0.02$, but failed to alter the ratio in the severely ischemic zone.

### *Control experiments*

In the 12 dogs that underwent coronary occlusion but were given normal saline instead of propranolol, the changes from preocclusion control to occlusion were only significantly different from the changes observed in the 18 dogs subsequently treated with propranolol in that the control dogs exhibited greater increases in heart rate (Tables I–IV). However, there were important differences comparing the changes from the occlusion state to the occlusion plus propranolol state. In contrast to the results in propranolol treated dogs, in control dogs, (*a*) heart rate and LV dP/dt did not fall (Table I); (*b*) end-diastolic length did not rise (Table II); (*c*) stroke shortening and velocity did not fall in normal and moderately ischemic zones (Table II); (*d*) the extent of paradoxical bulging did not decrease (Table II); (*e*) regional flow did not fall in the normal zone or rise in the moderately and severely ischemic zone (Table IV).

## DISCUSSION

Coronary occlusion resulted in minor effects on overall LV function and function in the normal zone, but induced progressively greater impairment of function in moderately and severely ischemic segments. Propranolol then exerted relatively slight, but statistically significant, effects on regional function in normal, moderately, and severely ischemic zones. In normal segments and in the majority of ischemic segments that still shortened during systole, propranolol reduced the extent and velocity of shortening and segment work performed. In contrast, in those segments that paradoxically lengthened during systole, propranolol decreased the extent of paradoxical motion and post-systolic shortening of those segments (Fig. 4). This latter finding could be interpreted as an improvement in function, since the extent of passive stretching fell after propranolol, but could also merely reflect an interaction between ischemic and nonischemic portions of the heart and may not be directly related to an effect of the drug on the severely ischemic portion of the heart.

Propranolol's depressant action on overall function and function in the normal zone after coronary occlusion was predictable, and is consistent with the prior studies of Mueller et al. (8), and Liang and Hood (7). In contrast its action on ischemic segments could not have been predicted. Studies in open-chest anesthetized animals have shown both improvement (12) and depression of function (10) after beta adrenergic blockers. The study of Theroux et al. (11), conducted in conscious dogs supports that of Lekven (12) in that propranolol pretreatment reduced the impairment of function induced by coronary occlusion on marginally ischemic segments. As mentioned above, in the present study, propranolol administration in doses ranging from 0.5 to 2.0 mg/kg generally depressed function slightly in the presence of sustained coronary occlusion. It is important to point out that the depression induced by propranolol was trivial, e.g., in comparison with the depression induced by simple coronary occlusion (Fig. 2). Moreover, the depression observed in moderately ischemic zones was significantly less than that observed in normal zones.

One of the important differences in the results of this study conducted in conscious dogs and those conducted previously in anesthetized animals with an open chest is the extent to which propranolol reduced heart rate. A striking reduction is frequently observed in anesthetized, open-chest preparations, when propranolol is administered in the face of acute coronary occlusion (1, 2, 5, 6, 10, 13). In contrast heart rate fell by an average of only 8 beats/min after propranolol in the present study. If propranolol were to reduce heart rate considerably more, as occurs in anesthetized animals, a more favorable effect on function of ischemic myocardium may well have been observed. However, in the conscious, unsedated dog with myocardial ischemia, propranolol induces only a slight reduction in heart rate even when the ischemia is relatively large, as occurs with a left circumflex occlusion.

Failure of propranolol to reduce heart rate in the ischemic heart of conscious dogs was also observed by Liang and Hood (7), who suggested that the mechanism of the tachycardia of coronary occlusion was most likely due to withdrawal of vagal restraint. It is interesting to note in the study by Mueller et al. (8), that propranolol reduced heart rate in patients with acute myocardial infarction by an almost identical amount as was observed in the present study in conscious dogs.

While propranolol exerted significant effects on ischemic cardiac function, no significant effect was observed on the ST potential, which has been consistently shown to decrease in experiments conducted in open-chest anesthetized animals (1, 2, 5, 6, 10, 13). It is of interest that Bodenheimer et al. (10), found that the ST electrogram fell substantially in their open-chest anesthetized animals treated with propranolol after coronary occlusion when heart rate was allowed to fall, but returned to the prepropranolol, occlusion level, when the effects of decreased heart rate were eliminated by pacing. These data are consistent with ours, in that heart rate fell by only 8 beats/min in the present experiments, and the ST potential did not fall (Table III).

In the present study, the most striking effects of propranolol were on regional myocardial blood flow. As expected flow fell in normal zones, which probably reflected the reduction in myocardial $O_2$ demands induced by the reduction in myocardial contractility and work. In contrast, flow rose significantly in moderately and severely ischemic zones despite a reduction in cardiac work and contractility. The mechanism of the redistribution of coronary flow was not examined in the present study. It could have been due to shunting of blood flow from nonischemic to ischemic tissue. Another possible explanation is that forces acting on ischemic myocardium were diminished after propranolol, e.g., post-systolic shortening, thereby allowing more coronary filling. In the severely ischemic zone the redistribution of coronary flow did not favor either the endo or epicardial layers, but occurred transmurally, as reflected by no significant change in the ENDO/EPI ratio. In contrast in the moderately ischemic zone proportionally more flow went to the endocardium, since the ENDO/EPI ratio rose significantly.

Since flow to ischemic tissue can increase spontaneously with time due to opening of collaterals or primary channels from the nonoccluded arteries, it was considered important to conduct a series of control experiments, where saline instead of propranolol was administered. In these experiments flow to ischemic regions did not change significantly over the 10–15-minute period of occlusion studied (Table IV). This is consistent with measurements of regional myocardial function in the present investigation, which also did not change significantly over this 10–15-min period in the animals where ischemia was induced, but saline instead of propranolol, was administered (Table II). These findings are also consistent with prior studies both in conscious and anesthetized dogs. For instance Bishop et al. found that flow to ischemic myocardium did not change between 5 min and 6 h after occlusion in conscious dogs (23), whereas in anesthetized dogs Hirzel et al. (24) and Becker et al. (5) found little change in the central ischemic zone flow from 10 min to 24 h after occlusion in endocardial layers (24) and from 60 to 90 min after occlusion (5), respectively. In contrast, Rivas et al. found that flow to ischemic tissue increased from 45 s to 2 h after occlusion (25). However, the study by Rivas et al. (25) is not inconsistent with the present findings or those of Bishop et al. (23), Hirzel et al. (24), or Becker et al. (5), since all the studies except for that by Rivas et al. (25), made the initial flow determination at a later time after occlusion. Thus, it appears from the results of these studies as well as the control experiments conducted in the present investigation that some flow adjustments normally occur initially (during the first few minutes after occlusion), but the flow to ischemic tissue then remains relatively stable for at least several hours. Therefore, when flow changes significantly during the stable period, it most likely reflects a change induced by the intervention, e.g., propranolol, rather than a spontaneous occurrence.

Prior studies in open-chest anesthetized preparations consistently failed to demonstrate a change in flow to ischemic tissue with propranolol (4–6). Once again, while the results of experiments in anesthetized preparations are not consistent with those of the present study, it is interesting to note that the study by Mueller et al. (8) in patients observed an increase in coronary sinus $O_2$ tension after propranolol administration. There are two important hemodynamic differences in the response to propranolol in conscious and anesthetized, open-chest animals with acute myocardial ischemia. As noted above, propranolol elicits a much greater decrease in heart rate in anesthetized, open-chest preparations with acute myocardial ischemia (1, 2, 6, 10, 13). In addition propranolol induces greater dilation of the heart of the open-chest anesthetized animal, whereas end-diastolic cardiac size as determined by direct measurement of LV diameter is near maximal at rest in the conscious dog,[3] and thus can only increase slightly with propranolol, as was observed in these experiments.

In summary, propranolol induced a significant redistribution of myocardial blood flow in the ischemic

[3] Boettcher, D. H., S. F. Vatner, G. R. Heyndrickx, and E. Braunwald. Extent of utilization of the Frank-Starling mechanism in control of cardiac performance in the conscious dog. Submitted for publication.

heart with flow falling in normal zones and rising in moderately and severely ischemic zones. This improvement in flow occurred concomitantly with a depression of cardiac function and work and extent of paradoxical bulging or passive stretching in severely ischemic segments. This study suggests two possible salutary actions for propranolol in the treatment of ischemic heart disease where cardiac decompensation is not also a factor. The slight decreases in cardiac rate and contractility should exert an $O_2$ sparing effect on ischemic myocardium, as long as cardiac failure is not present. This coupled with an increase in blood flow to ischemic tissue could result in protection of ischemic myocardium (1–3) and prove to be beneficial for patients with acute myocardial ischemia.

## ACKNOWLEDGMENTS

This work was supported, in part, by grants HL 17459, HL 17665, and HL 15416 from the U. S. Public Health Service.

## REFERENCES

1. Maroko, P. R., J. K. Kjekshus, B. E. Sobel, T. Watanabe, J. W. Covell, J. Ross, Jr., and E. Braunwald. 1971. Factors influencing infarct size following experimental coronary artery occlusions. *Circulation.* **43:** 67–82.
2. Shatney, C. H., D. J. Maccarter, and R. C. Lillehei. 1976. Effects of allopurinol, propranolol and methylprednisolone on infarct size in experimental myocardial infarction. *Am. J. Cardiol.* **37:** 572–580.
3. Reimer, K. A., M. M. Rasmussen, and R. B. Jennings. 1973. Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. *Circ. Res.* **33:** 353–363.
4. Pitt, B., and P. Craven. 1970. Effect of propranolol on regional myocardial blood flow in acute ischaemia. *Cardiovasc. Res.* **4:** 176–179.
5. Becker, L. C., R. Ferreira, and M. Thomas. 1975. Effect of propranolol and isoprenaline on regional left ventricular blood flow in experimental myocardial ischaemia. *Cardiovasc. Res.* **9:** 178–186.
6. Kloner, R. A., K. A. Reimer, and R. B. Jennings. 1976. Distribution of coronary collateral flow in acute myocardial ischaemic injury: Effect of propranolol. *Cardiovasc. Res.* **10:** 81–90.
7. Liang, C-S., and W. B. Hood, Jr. 1974. The myocardial depressant effect of beta-receptor blocking agents. Comparative study of DL-propranolol, D-propranolol, and practolol in awake dogs with and without acute myocardial infarction. *Circ. Res.* **35:** 272–280.
8. Mueller, H. S., S. M. Ayres, A. Religa, and R. G. Evans. 1974. Propranolol in the treatment of acute myocardial infarction. Effect on myocardial oxygenation and hemodynamics. *Circulation.* **49:** 1078–1087.
9. Kerber, R. E., and D. C. Harrison. 1971. Contraindications and limitations of beta adrenergic blockade in clinical medicine. Circulatory effects and clinical uses of beta-adrenergic blocking drugs. *Excerpta Med. Int. Congr. Ser.* 131–138.
10. Bodenheimer, M. M., V. S. Banka, and R. H. Helfant. 1976. Propranolol in experimental myocardial ischemia: Dissociation of effects on contraction and epicardial ST segments. *Am. Heart J.* **92:** 481–486.
11. Theroux, P., J. Ross, Jr., D. Franklin, W. S. Kemper, and S. Sasayama. 1976. Regional myocardial function in the conscious dog during acute coronary occlusion and responses to morphine, propranolol, nitroglycerin, and lidocaine. *Circulation.* **53:** 302–314.
12. Lekven, J. 1975. Effect of practolol on left ventricular dimensions during coronary occlusion. *Am. J. Cardiol.* **36:** 179–184.
13. Wendt, R. L., R. C. Canavan, and R. J. Michalak. 1974. Effects of various agents on regional ischemic myocardial injury: Electrocardiographic analysis. *Am. Heart J.* **87:** 468–482.
14. Manders, W. T., and S. F. Vatner. 1976. Effects of sodium pentobarbital anesthesia on left ventricular function and distribution of cardiac output in dogs, with particular reference to the mechanism for tachycardia. *Circ. Res.* **39:** 512–517.
15. Vatner, S. F., and N. T. Smith. 1974. Effects of halothane on left ventricular function and distribution of regional blood flow in dogs and primates. *Circ. Res.* **34:** 155–167.
16. Franklin, D. E., N. W. Watson, K. E. Pierson, and R. L. Van Citters. 1966. Technique for radio telemetry of blood-flow velocity from unrestrained animals. *Am. J. Med. Electron.* **5:** 24–28.
17. Vatner, S. F., D. Franklin, and R. L. VanCitters. 1970. Simultaneous comparison and calibration of the Doppler and elegromagnetic flowmeters. *J. Appl. Physiol.* **29:** 907–910.
18. Patrick, T. A., S. F. Vatner, W. S. Kemper, and D. Franklin. 1974. Telemetry of left ventricular diameter and pressure measurements in unrestrained animals. *J. Appl. Physiol.* **37:** 276–281.
19. Vatner, S. F., R. W. Millard, T. A. Patrick, and G. R. Heyndrickx. 1976. Effects of isoproterenol on regional myocardial function, electrogram, and blood flow in conscious dogs with myocardial ischemia. *J. Clin. Invest.* **57:** 1261–1271.
20. Domenech, R. J., J. I. E. Hoffman, M. I. M. Nobel, K. B. Saunders, J. R. Henson, and S. Subijanto. 1969. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anesthetized dogs. *Circ. Res.* **25:** 581–596.
21. Millard, R. W., H. Baig, and S. F. Vatner. 1977. Cardiovascular effects of radioactive microsphere suspensions and Tween 80 solutions. *Am. J. Physiol.* **1:** H331–334.
22. Snedecor, G. W., and W. G. Cochran. 1967. Statistical Methods. Iowa State University Press, Ames, Iowa. 6th edition. 91–98.
23. Bishop, S. P., F. C. White, and C. M. Bloor. 1976. Regional myocardial blood flow during acute myocardial infarction in the conscious dog. *Circ. Res.* **38:** 429–438.
24. Hirzel, H. O., G. R. Nelson, E. H. Sonnenblick, and E. S. Kirk. 1976. Redistribution of collateral blood flow from necrotic to surviving myocardium following coronary occlusion in the dog. *Circ. Res.* **39:** 214–222.
25. Rivas, F., F. R. Cobb, R. J. Bache, and J. C. Greenfield, Jr. 1976. Relationship between blood flow to ischemic regions and extent of myocardial infarction. Serial measurement of blood flow to ischemic regions in dogs. *Circ. Res.* **38:** 439–447.