Effects of Nitroglycerin and Propranolol on the Distribution of Transmural Myocardial Blood Flow during Ischemia in the Absence of Hemodynamic Changes in the Unanesthetized Dog

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ABSTRACT Chronically instrumented awake dogs were used to study the effects of nitroglycerin and propranolol on the transmural distribution of myocardial blood flow during transient ischemia. Studies were carried out 7–14 d after implantation of an electromagnetic flowmeter probe and balloon occluder on the left circumflex coronary artery, placement of epicardial minor axis sonar crystals, and implantation of left atrial, left ventricular, and aortic catheters. The occluder was inflated to completely interrupt flow for 10 s followed by partial release to reestablish flow at 60% of the preocclusion level. During this partial release, which served as the control for the study, regional myocardial blood flow was measured with 7- to 10-μm radioactive microspheres. After control measurements, seven dogs were given nitroglycerin (0.4 mg i.v.) and eight dogs propranolol (0.2 mg/kg i.v.). 5 min later the occlusion and partial release sequence was repeated, and regional myocardial blood flow was measured when heart rate, aortic and left ventricular end-diastolic pressure, and minor axis diameter were unchanged from control values.

The data values were selected so that total flow to the ischemic region during partial release after nitroglycerin or propranolol administration was not significantly different from flow during the control partial release. After nitroglycerin administration, endocardial flow (endo) in the ischemic region increased from 0.46±0.07 to 0.59±0.06 ml/min per g ($P < 0.006$); epicardial flow (epi) decreased from 0.78±0.09 to 0.70±0.08 ml/min per g ($P < 0.04$). The endo:epi ratio increased from 0.65±0.07 to 0.92±0.10 ($P < 0.05$). In contrast, administration of propranolol produced no significant change in transmural flow (endo, 0.42±0.02 and 0.46±0.03 ml/min per g; epi, 0.71±0.06 and 0.70±0.07 ml/min per g) or in the endo:epi ratio (0.60±0.03, 0.66±0.06) in the ischemic region.

Nitroglycerin and propranolol produce different effects on the transmural distribution of blood flow to ischemic myocardium. Nitroglycerin can increase blood flow to the underperfused endocardium in the absence of alterations in heart size, hemodynamic parameters, and total transmural flow to the ischemic region. Under similar conditions, propranolol has no significant effect on the transmural distribution of blood flow to an ischemic region.

INTRODUCTION

Nitroglycerin and propranolol are firmly established as clinically effective antianginal agents, but their mechanism of action remains controversial. During angina, a transmural maldistribution of blood flow exists, resulting in subendocardial ischemia (1–3). The ischemia may be reduced by decreasing oxygen consumption in the ischemic area or by increasing blood flow to the ischemic region. If contractility remains constant, myocardial oxygen demand can be lessened by altering the hemodynamic state, i.e., by lowering the heart rate or reducing ventricular systolic wall tension. Nitroglycerin produces systemic venous dilatation, leading to a decrease in ventricular volume secondary to a decrease in venous return (4) and also may decrease systemic arterial pressure. Either of these

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actions may reduce systolic wall tension and myocardial oxygen demand (5). Myocardial oxygen consumption can be decreased by propranolol through a reduction in heart rate (6).

The other way in which nitroglycerin and propranolol may produce relief of angina is by increasing blood flow to the ischemic area. This can be accomplished either by increasing collateral flow, resulting in an increase in total myocardial flow, or by redistributing transmural flow within the ischemic area without increasing total transmural flow to the region. Redistribution of flow can result directly from vasodilatation of coronary vessels supplying the ischemic subendocardium. If this occurs, flow to the subepicardium will decrease and flow to the subendocardium will increase. This redistribution also could be produced indirectly by a decrease in left ventricular diastolic wall tension, resulting in a decrease in diastolic impedance to subendocardial flow. Previous studies in both open- and close-chested dogs have examined the effects of nitroglycerin (7–13) and propranolol (13–18) on myocardial blood flow to ischemic regions, but have not determined whether alteration in flow was the result of a direct effect on the coronary vasculature or of changes in heart size and hemodynamic parameters.

The purpose of this study was to determine whether nitroglycerin and propranolol could exert a direct effect on the transmural coronary vasculature. The effect of each drug on the transmural distribution of myocardial blood flow during periods of transient ischemia was examined in the absence of changes in total flow to the ischemic region and with hemodynamic parameters held constant. The study was performed in chronically instrumented, unanesthetized dogs to eliminate the effects of general anesthesia and acute surgical trauma on the regulation of coronary blood flow.

METHODS

15 adult, mongrel dogs, weighing 23–30 kg, were anesthetized with an intravenous bolus of sodium thiamylal (30–40 mg/kg), and underwent left thoracotomy. Polyvinyl chloride heparin-filled catheters, 3 mm in diameter, were introduced into the ascending aorta through the left internal mammary artery, into the left atrial cavity through the left atrial appendage, and into the left ventricular cavity via a stab wound through the apex of the heart. A matched pair of 5-mm piezoelectric epicardial ultrasonic dimension crystals were sutured across the minor axis of the heart, one on the anterior free wall of the left ventricle and the other on the posterior free wall midway between the apex and base of the heart. The proximal 1.5 cm of the circumflex branch of the left coronary artery was dissected free, and an electromagnetic flowmeter probe (Howell Instruments, Inc., Camarillo, Calif.) was positioned around the vessel. An inflatable hydraulic occluder, constructed in our laboratory, was placed around the circumflex vessel just distal to the flowmeter probe. Coronary flow could be accurately controlled by inflation and deflation of the occluder. An epicardial bipolar pacing electrode was sutured to the right atrial appendage. The catheters, sonar crystal leads, flowmeter probe leads, occluder tubing, and pacing leads were tunneled through the chest wall and placed in a dorsal subcutaneous pouch at the base of the neck. The thoracotomy incision was closed, and the animals allowed to recover.

Studies were carried out 7–14 d after the initial surgery, when the animals were active, fully recovered from surgery, and free from fever and anemia. On the morning of the study, each animal received an intramuscular injection of 10–20 mg of morphine sulfate at least 2 h before any measurements. The subcutaneous pouch was infiltrated with 1% lidocaine hydrochloride, and the catheters and leads brought out through a small incision. The aortic and left ventricular pressure catheters were connected to Statham P23Db transducers (Statham Instruments, Inc., Oxnard, Calif.), and the zero reference level was the midchest level. The ultrasonic minor axis crystal pair was connected to a sonomicrometer, and crystal separation sampled at 1 kHz and converted to an analogue voltage output as described (19). The system was calibrated by substituting pulses of known duration from a crystal-controlled pulse generator into the circuit. Phasic and mean circumflex coronary flow were measured with a Statham M-4000 flowmeter (Statham Instruments, Inc.). Flowmeter calibrations were performed by passing measured flows of normal saline through the probes, and calibration remained within a SD of 4% during the study. All data were recorded with a Hewlett-Packard model 8800 8-channel direct-writing oscillograph and a Hewlett-Packard model 3917-A 8-channel magnetic tape recorder (Hewlett-Packard Co., Palo Alto, Calif.).

Regional myocardial blood flow was estimated by injecting 7- to 10-μm carbonized microspheres labeled with the gamma-emitting radionuclides ^{141}Ce, ^{51}Cr, ^{85}Sr, ^{46}Sc, ^{125}I, and ^{95}Nb into the left atrium. Microspheres were obtained as 1.0 mCi of each nuclide in 10 ml of 10% dextran. This stock solution was diluted in 10% dextran so that 1.0 ml contained 3,000,000 microspheres. The microspheres were mixed before injection by alternate agitation for at least 15 min in an ultrasonic bath and a Vortex agitator (Scientific Industries, Inc., Bohemia, N. Y.). Complete dispersion of microspheres was verified by examining a drop of microsphere suspension with a light microscope. In each dog, blood flow measurements were made with 1.0 cm^3 of suspension injected over a 5-s interval into the left atrial catheter and the catheter flushed with 5 cm^3 of normal saline. A reference sample of arterial blood was collected from the aortic catheter at a constant rate of $\cong$17 ml/min by a withdrawal pump, beginning simultaneously with the microsphere injection and continuing for 90 s.

The laboratory was dimly lit and kept free of noise and extraneous activity. The animals were allowed at least 30 min to become further accustomed to the laboratory after the instrumentation was connected and before measurements were undertaken. Control hemodynamic measurements, consisting of minor axis dimension, aortic and left ventricular pressures, and phasic and mean left circumflex coronary blood flow, were then made. The balloon occluder was rapidly inflated to occlude the circumflex coronary artery for 10 s and then rapidly deflated. Only those dogs with adequate resultant reactive hyperemic responses (debt repayment > 400%) were included in this study.

After a steady state was reached, a 10-s circumflex coronary artery occlusion was produced. At the end of 10 s, the balloon occluder was partially deflated to allow flow to reach $\cong$60% of control level. Flow was allowed to stabilize over a 2- to 3-s period and then 1 cm^3 of microsphere solution, labeled with a radionuclide, was injected into the left atrium. The partial release was maintained for at least 90 s while the reference sample blood was withdrawn; the occlusion then was released. This sequence of occlusion and

partial release was repeated with one or two differently labeled microspheres at least 10 min apart.

The measurements obtained during the partial release represent the control data before drug administration. The dogs then were divided into two groups.

Group 1. In this group of seven dogs, a freshly prepared solution of 0.4 mg of nitroglycerin in 5 cm^3 of normal saline was administered intraveneously over 60 s. Approximately 5 min after nitroglycerin infusion, when the slight changes in heart rate and blood pressure had returned to control levels for at least 2 min, a 10-s occlusion and partial release of the occlusion to ≅60% of the control value was performed again, and radionuclide-labeled microspheres injected as soon as a stable level of flow was attained. The partial occlusion was released after collection of the reference blood sample was completed. After a 15-min interval, this sequence of nitroglycerin administration, occlusion, and partial release was repeated with a solution of another nuclide-labeled microsphere.

Group 2. Eight dogs received an intravenous bolus of 0.2 mg/kg of propranolol after the control measurements were made. Hemodynamic variables were measured 10 min after propranolol administration. In two dogs, a decrease in heart rate of 8 and 10 beats/min, respectively, was observed, and the heart was paced to a rate identical to that obtained during the control state. A 10-s occlusion was then produced, followed by a partial release of the occluder to allow flow to reach the same level as during the partial release before propranolol administration. A microsphere injection was performed when a stable level of flow was reached. This sequence of occlusion, partial release, and microsphere injection was repeated within 20 min of propranolol administration. After the last microsphere injection, three animals received isoproterenol, 1.5 μg/min i.v., to test beta blockade; no change in heart rate occurred.

Combined data. The animals were sacrificed at the end of data collection by intravenous administration of 30 mg/kg sodium thiamylal followed by 40 meq of potassium chloride. The hearts were removed, the flowmeter probe and sonar crystals dissected free, and each heart fixed in 10% buffered formalin for at least 24 h. The atria, right ventricle, aorta, and large epicardial blood vessels were dissected from the left ventricle and discarded. The left ventricle was sectioned into four transverse rings as described (20). The rings were divided radially into six anatomic sections corresponding to the anterior papillary muscle, anterior free wall, septum, posterior free wall, posterior papillary muscle, and lateral free wall. These sections were subdivided into four transmural layers of approximately equal weight from the epicardium to the endocardium. Each tissue sample then was weighed and placed in a separate plastic vial for subsequent gamma counting.

To achieve the maximum fidelity in counting the samples, separate vials containing a solution with ≅10,000 counts of a single radionuclide-labeled microsphere were placed in the counting chamber of a Packard model A5912 gamma spectrophotometer (Packard Instrument Co., Inc., Downers Grove, Ill.). The energy counting windows were set for each isotope employing a video display to optimize the number of counts while minimizing the spillover contaminant activity from the other isotopes. A matrix was constructed using the counts recorded in all windows from each isotope. This matrix counted the fraction of contaminant contributed to each window by the other isotopes. Raw counts of the individual isotopes were obtained in each of the myocardial and reference blood samples. A system of simultaneous linear equations was solved with an IBM model 1130 digital computer (IBM Corp., White Plains, N. Y.) to correct the raw counts for contaminant activity from the other isotopes. Flow to each area of the myocardium in milliliters per minute was calculated by using the formula: $Q_m = Q_r \cdot C_m/C_r$, where Q_m is myocardial flow (milliliters per minute), Q_r is reference blood flow (milliliters per minute), C_m is count activity in the isotope sample, and C_r is count activity in reference blood flow samples. Myocardial tissue sample blood flow (milliliters per minute) was divided by the appropriate sample weight and expressed as milliliters per minute per gram. Tissue samples from the anterior regions of the left ventricle were averaged to estimate both transmural and total flow to the nonischemic region.

Heart rate, aortic and left ventricular pressures, minor axis diameter, and circumflex flow were measured from the graphic output obtained at the time of microsphere injection. These data were averaged over a 20-s period beginning at the time of the partial deflation of the balloon occluder after total occlusion. Data pairs were chosen so that heart rate, aortic and left ventricular pressures, and minor axis systolic and diastolic diameters after drug administration were within 10% of control values.

The effect of each drug on the transmural distribution of flow was examined. Data values were paired so that total ischemic region flow after drug administration did not differ by >0.07 ml/min per g from the ischemic region flow during the control period. This difference was within the experimentally determined error of the microsphere blood flow measurement method.[1]

RESULTS

Group 1. Fig 1 shows a representative tracing of the phasic and mean hemodynamic data recorded continuously during a control period, a complete occlusion, and a partial release. Heart rate, aortic and left ventricular blood pressures, and left ventricular systolic and diastolic minor axis external diameters measured in the seven dogs in group 1 during the partial release phase of coronary flow are shown in Table I. Data obtained during the partial release phase after nitroglycerin administration were not significantly different from those obtained during the control partial release.

The transmural distribution of regional myocardial blood flow in the seven dogs during the partial release phase is shown in Table II. Mean flow to the nonischemic region was not altered by nitroglycerin (0.77±0.08 and 0.69±0.06 ml/min per g). Endocardial flow before and after nitroglycerin (0.82±0.09 and 0.75±0.07 ml/min per g) and epicardial flow before and after nitroglycerin (0.62±0.06 and 0.55±0.04 ml/

[1] Six different nuclide-labeled microspheres were injected simultaneously into six dogs during acute occlusion of the left circumflex coronary artery to produce regions of widely varying blood flow. Regional flow was computed separately for each of the six microspheres. The standard deviation for simultaneous measurement of regional flow was determined as a function of the mean value for the six determinations of flow and found to be: SD = ±(0.007 + 0.029 [flow] + 0.002 [flow]²) ml/min per g. For a representative ischemic flow of 0.25 ml/min per g, the range of error is ±0.02 ml/min per g, and the SD is ±0.01 ml/min per g.

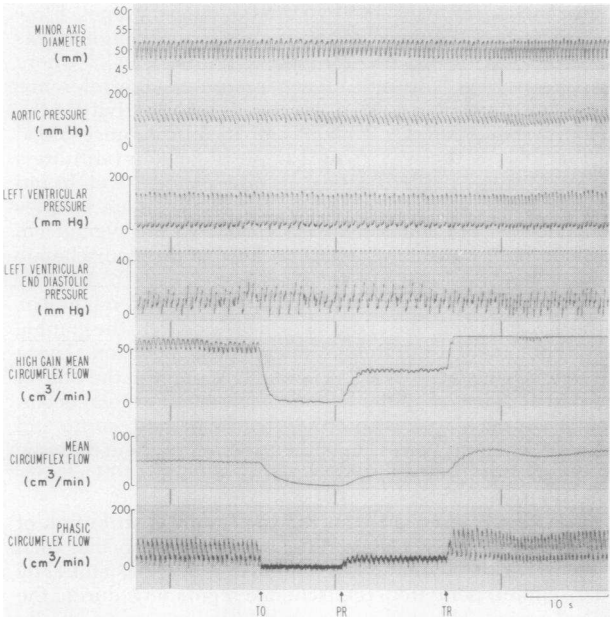

FIGURE 1 The simultaneous recording of left ventricular minor axis diameter, aortic pressure, left ventricular end-diastolic pressure, and phasic and mean left circumflex coronary flow are shown during control, total coronary occlusion (TO), partial release of the coronary occlusion (PR), and total release (TR).

min per g) were unchanged. The endocardial:epicardial blood flow ratio of the nonischemic region also was not altered by nitroglycerin (1.34±0.06 and 1.39±0.04 ml/min per g).

Mean flow to the total ischemic region was 0.67±0.08 ml/min per g during the control period and 0.69±0.07 ml/min per g after nitroglycerin administration. Endocardial flow to the ischemic region increased from 0.46±0.07 to 0.59±0.06 ml/min per g with nitroglycerin ($P < 0.006$). Nitroglycerin decreased epicardial flow from 0.78±0.09 to 0.70±0.08 ml/min per g ($P < 0.04$). The endocardial:epicardial blood flow ratio of the ischemic region increased after nitroglycerin administration from 0.65±0.07 to 0.92±0.10 ml/min per g ($P < 0.05$).

Group 2. Heart rate, left ventricular and aortic pressures, and left ventricular minor axis diameters during the restricted inflow period for the eight dogs in group 2 are shown in Table III. No significant changes were seen in any hemodynamic parameters after propranolol administration while the animals were paced to the control rate.

Regional myocardial blood flow distribution in the nonischemic and ischemic regions during the partial release phase are shown in Table IV. Mean flow to the nonischemic region was not changed by propranolol (0.86±0.07 and 0.83±0.06 ml/min per g). Propranolol did not significantly alter endocardial flow (0.96±0.08 and 0.95±0.08 ml/min per g), epicardial flow (0.64 ±0.07 and 0.61±0.04 ml/min per g), or the endocardial:epicardial flow ratio (1.54±0.10 and 1.68±0.15).

Mean flow to the ischemic region was not different after propranolol (0.63±0.03 and 0.66±0.04 ml/min per g). Propranolol did not change endocardial flow (0.42±0.02 and 0.46±0.03 ml/min per g), epicardial flow (0.71±0.06 and 0.70±0.07 ml/min per g), or the endocardial:epicardial blood flow ratio (0.60±0.03 and 0.66±0.06).

DISCUSSION

No consensus exists concerning the effects of nitroglycerin and propranolol on myocardial blood flow and the coronary vasculature. During transient ischemia, one mechanism by which blood flow to the myocardium can be increased is by increasing flow through collateral vessels. With open-chested dogs, Fam and McGregor (7) found that nitroglycerin increased collateral flow only if well-developed collateral vessels already existed. No increase in collateral flow was ob-

TABLE I
Hemodynamic Measurements: Group 1

	Heart rate	Aortic pressure		Left ventricular		
		Systolic	Diastolic	End-diastolic pressure	End-diastolic external diameter	End-systolic external diameter
	bpm	*mm Hg*	*mm Hg*	*mm Hg*	*mm*	*mm*
Control	78±8	113±4	80±2	9±1	61±3	55±3
Nitroglycerin	75±6	110±4	78±2	9±1	61±3	54±3
P value	NS	NS	NS	NS	NS	NS

Hemodynamic and dimension measurements during the partial release phase of coronary flow before and after nitroglycerin administration (group 1; $n = 7$). All values mean±SEM. NS denotes *P* value >0.05 between control and postnitroglycerin values.

TABLE II
Regional Myocardial Blood Flow and Endocardial:Epicardial Flow Ratios: Group 1

	Total flow	Left ventricular layers				Endocardial:Epicardial ratio
		1	2	3	4	
	ml/min/g					
Nonischemic region						
Control	0.77±0.08	0.62±0.06	0.79±0.09	0.84±0.09	0.82±0.09	1.34±0.06
Nitroglycerin	0.69±0.06	0.55±0.04	0.69±0.07	0.76±0.07	0.75±0.07	1.39±0.04
P value	NS	NS	NS	NS	NS	NS
Ischemic region						
Control	0.67±0.08	0.78±0.09	0.79±0.11	0.70±0.12	0.46±0.07	0.65±0.07
Nitroglycerin	0.69±0.07	0.70±0.08	0.77±0.09	0.72±0.07	0.59±0.06	0.92±0.10
P value	NS	<0.04	NS	NS	<0.006	<0.05

Regional myocardial blood flow and endocardial:epicardial blood flow ratios during the partial release phase of coronary flow before and after nitroglycerin administration (group 1). All values mean±SEM. NS denotes *P* value >0.05 between control and postnitroglycerin values.

served with acute coronary artery ligation. Capurro et al. (12) also demonstrated an increase in collateral flow after the administration of nitroglycerin in open-chested animals with well-developed coronary collaterals. Mathes and Rival (8) and Cohen et al. (9) found no increase in collateral flow after acute coronary occlusion in open-chested dogs. Bache et al. (10), with conscious, resting dogs, similarly reported no change in total coronary blood flow to the ischemic region after total coronary occlusion. In contrast, Becker (11) found an increase in collateral flow to the ischemic area after nitroglycerin administration and coronary ligation.

The reported effects of propranolol on coronary collateral flow also conflict. Previous studies (13–17) in open-chested preparations have failed to demonstrate an increase in collateral flow to ischemic myocardium after acute total coronary occlusion. Studies by Vatner et al. (18) in conscious animals demonstrated an increase in collateral flow after total coronary occlusions of 15–40 min.

An alternate mechanism by which blood flow to the ischemic areas can be augmented is by the transmural redistribution of coronary flow. In the presence of subendocardial ischemia, nitroglycerin has been demonstrated to cause a redistribution of flow away from the epicardium and toward the endocardium by Becker et al. (13) in open-chested dogs and by Bache et al. (10) in conscious animals. Becker et al. (13) also observed a redistribution of flow toward the endocardium during ischemia after propranolol administration.

To assess the direct effects of nitroglycerin and propranolol on coronary vasculature, the changes in hemodynamics secondary to the peripheral effects of each drug must be eliminated, because changes in left

TABLE III
Hemodynamic Measurements: Group 2

	Heart rate	Aortic pressure		Left ventricular		
		Systolic	Diastolic	End-diastolic pressure	End-diastolic external diameter	End-systolic external diameter
	bpm	*mm Hg*	*mm Hg*	*mm Hg*	*mm*	*mm*
Untreated	93±8	119±6	81±3	7±1	55±3	50±3
Propranolol	90±7	124±5	84±6	7±1	55±3	50±3
P value	NS	NS	NS	NS	NS	NS

Hemodynamic and dimension measurements during the partial release phase of coronary flow before and after propranolol administration (group 1; $n = 8$). All values mean±SEM. NS denotes *P* value >0.05 between control and postpropranolol values.

TABLE IV

Regional Myocardial Blood Flow and Endocardial/Epicardial Flow Ratios: Group 2

	Total flow	Left ventricular layers				Endocardial:Epicardial ratio
		1	2	3	4	
	ml/min/g					
Nonischemic region						
Control	0.86±0.07	0.64±0.07	0.88±0.08	0.94±0.09	0.96±0.08	1.54±0.10
Propranolol	0.83±0.06	0.61±0.04	0.84±0.06	0.91±0.07	0.95±0.08	1.68±0.15
P value	NS	NS	NS	NS	NS	NS
Ischemic region						
Control	0.63±0.03	0.71±0.06	0.75±0.05	0.61±0.02	0.42±0.02	0.60±0.03
Propranolol	0.66±0.04	0.70±0.07	0.81±0.05	0.66±0.03	0.46±0.03	0.66±0.06
P value	NS	NS	NS	<0.02	NS	NS

Regional myocardial blood flow and endocardial:epicardial blood flow ratios during the partial release phase of coronary flow before and after propranolol administration (group 2). All values mean±SEM. NS denotes *P* value >0.05 between control and postpropranolol values.

ventricular filling pressure, aortic pressure, heart size, and heart rate can exert profound effects on regional myocardial blood flow. In the previously cited studies, hemodynamic parameters and heart size were not held constant after drug administration. To examine the effects of nitroglycerin and propranolol on the transmural distribution of flow during ischemia, total flow to the ischemic region must be held constant. Therefore, the present study was designed to examine the specific effects of nitroglycerin and propranolol on ischemic myocardial blood flow distribution. This was carried out during a period when neither total flow to the ischemic region nor hemodynamic parameters and heart size varied from conditions that existed before drug administration.

In the experimental model employed in this study, total left circumflex coronary artery occlusion produced maximum vasodilatation of the precapillary sphincters in the affected myocardium, and partial return of flow resulted in a redistribution of flow toward the subepicardium with resultant subendocardial ischemia. Since hemodynamic variables and ischemic area flow after drug administration were matched to levels obtained before the infusion of the drug, any changes in the transmural distribution of blood flow can be attributed only to a direct effect of nitroglycerin or propranolol on the coronary vasculature.

The results of this study demonstrate that nitroglycerin affects the transmural distribution of myocardial blood flow during ischemia. A possible mechanism by which nitroglycerin exerts its effect is through dilatation of the large transmural penetrating coronary vessels. Myocardial ischemia results in vasodilatation of the precapillary resistance vessels of the subendocardium and subepicardium (21, 22), but not of the larger conductive vessels. Fulton (23) observed the presence of large transmural penetrating vessels which conduct blood from the epicardial surface across the wall of the ventricle to the endocardium. Winbury et al. (21) have presented evidence that these transmural penetrating vessels do not participate in metabolic autoregulation and are not maximally vasodilated with ischemia. When resistance at the level of the precapillary vessels is decreased by ischemia, transmural penetrating vessels become a flow-limiting resistance to subendocardial perfusion. Because nitroglycerin has been shown to produce prolonged vasodilatation of the larger coronary conductive vessels, the redistribution of myocardial flow toward the ischemic myocardium can be attributed to a direct effect on these transmural penetrating vessels.

A second finding of this study is that propranolol does not alter the transmural distribution of blood flow in either normal or ischemic tissue. Previous measurements in nonischemic open-chested dogs indicated that propranolol did increase endocardial perfusion, while at the same time decreasing epicardial blood flow (24–25). The explanation for this finding was that beta blockade unmasked alpha receptors present in high concentrations in the epicardium leading to epicardial vasoconstriction and redistribution of transmural flow. In studies by Gross and Winbury (25), the heart rate in dogs was not allowed to decrease after propranolol, and no change in endocardial-epicardial blood flow distribution could be demonstrated. In the presence of ischemia, no redistribution of flow has been demonstrated in either open-chested (14) or conscious (18) animals, even when alterations occurred in heart rate and other hemodynamic variables. Therefore, the results of this study are consistent with previous measurements and indicate that propranolol does not exert a direct effect on the transmural penetrating arteries.

The results of the present study do not eliminate the possibility that propranolol may directly affect the coronary collateral vasculature.

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