Role of Propranolol in Improvement of the Relationship between O₂ Supply and Consumption in an Ischemic Region of the Dog Heart

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ABSTRACT Several aspects of the myocardial O₂ supply/consumption relationship were determined after coronary artery occlusion and subsequent β -adrenergic blockade in 16 anesthetized open-chest dogs. Small artery and vein O₂ saturations, and hence extraction, were obtained microspectrophotometrically and combined with radioactive microsphere blood flow determinations to calculate regional myocardial O₂ consumption. Eight dogs remained untreated after coronary artery ligation while another group was given 2 mg/kg propranolol, 10 min after occlusion. Untreated occlusion resulted in decreased arterial and especially venous O₂ saturations, indicating an increased O₂ extraction. Ischemic O₂ consumption was reduced and the subendocardial/subepicardial consumption ratio was reversed (1.26 vs. 0.37) due to the pattern of occluded area flow. Calculated O₂ supply/consumption also decreased. Propranolol produced no significant changes in volume or distribution of flow within the ischemic region while reducing flow, extraction, and consumption in the unoccluded region. The heterogeneity of arterial and particularly venous O₂ saturations within the ischemic region decreased dramatically. Venous O₂ saturations were elevated relative to the control group resulting in a reduced O₂ extraction. The decrease in heterogeneity of arterial and venous O₂ saturations suggest that propranolol eliminates microregions of relatively high O₂ extraction, consumption, and/or a majority of vessels with extremely low flow. This leads to a significant improvement in the O₂ supply/consumption ratio in the ischemic myocardium of the dog. This may be due to a reduction in the heterogeneity and level of β_1 -adrenergic receptor activity within the heart.

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INTRODUCTION

Coronary artery ligation results in extensive changes in pump function, blood flow, metabolism, and oxygen supply/demand balance in the affected region of the myocardium. Decreased systolic fiber shortening (1), increased anaerobic metabolites (2, 3), microvascular damage (4, 5), and decreased blood flow, especially in the subendocardium (6), are all characteristics of the ischemic or infarcted region. Decreased mitochondrial respiration (7), tissue PO₂ (8), and increased O₂ extraction as well as decreased O₂ consumption (9, 10) indicate alterations in O₂ availability and demand. Recent work has shown substantial variability of small artery and vein saturations as well as heterogeneous regions of O₂ extraction and consumption within the center of an ischemic zone caused by coronary artery ligation (11).

It has been demonstrated that propranolol causes a reduction in the extent of myocardial necrosis caused by short-term coronary artery ligation (12). Improvements in regional fiber shortening (13), high energy phosphate stores (14), and cellular damage (15) also occur within the ischemic tissue. The drug appears to decrease nonischemic perfusion (16) while producing variable effects on the volume and distribution of ischemic blood flow (17–20). The mechanism of the drug's protective effect, however, has not been fully elucidated.

This study was designed to determine the effect of propranolol on regional O₂ supply and consumption in control and ischemic areas of the left ventricle. Microspectrophotometric observations of small regional arteries and veins in quick-frozen hearts were made to determine regional O₂ extraction and were combined with regional measurements of blood flow with radioactive microspheres to determine regional

myocardial O_2 consumption and the O_2 supply/consumption ratio (21–24).

METHODS

Experiments were performed on 16 adult mongrel dogs between 14 and 27 kg in weight that were anesthetized with sodium pentobarbital (30 mg/kg, iv). The trachea was intubated, and artificial ventilation was instituted with a Harvard respiratory pump (Harvard Apparatus Co., Inc., S. Natick, MA). Ventilation was adjusted to maintain end-tidal CO_2 constant. An abdominal aortic catheter was inserted via the femoral artery before a left thoracotomy at the fifth interspace. A pericardial cradle was formed and the left anterior descending coronary artery (LAD)¹ was isolated and a tie placed around it below at least one major diagonal branch. Catheters were inserted in the left atrium for radioactive microsphere injections and in the left ventricle for measurement of left ventricular pressure and maximal positive derivative of pressure with respect to time (dP/dt). A catheter was also inserted in the right external jugular vein and advanced at least 2 cm into the coronary sinus. An interval of 30 min was provided for the preparation to stabilize.

Control heart rate, blood pressures, and dP/dt were recorded on a Beckman R 411 recorder (Beckman Instruments, Inc., Fullerton, CA). Anaerobic arterial and coronary sinus blood samples were analyzed for PO_2 , PCO_2 , and pH with blood gas analyzer model-113 (Instrumentation Laboratory, Inc., Lexington, MA). Hemoglobin concentration was determined with a Fisher hemophotometer (Fisher Scientific Co., Pittsburgh, PA). Thus, all dogs had control hemodynamic and blood samples taken before further treatment.

8 of the 16 dogs constituted an untreated group in which the previously isolated LAD was tied off. After 2 h, hemodynamic parameters and blood gas determinations were made. In addition, regional blood flow determinations were made using radioactively labeled microspheres. A reference blood sample was withdrawn from the femoral catheter at a constant rate of 7 ml/min. 30 s after initiation of withdrawal, a bolus of ~ 1 –2 million ^{141}Ce -labeled microspheres, Diam, $15 \pm 3 \mu$ (3 M Company, St. Paul, MN) was injected into the left atrial catheter and flushed with 3 ml of saline. The withdrawal of blood continued for a total of 2 min. The heart of the untreated dog was fibrillated, rapidly excised below the atrioventricular ring, and frozen in liquid nitrogen-cooled liquid propane within 10–15 s. The hearts were subsequently stored at $-70^\circ C$ for future analysis.

The second group of eight dogs was handled identically to that of the untreated group except that 10 min after LAD occlusion they were given a bolus injection of propranolol HCL (2 mg/kg). All other procedures performed after 2 h of occlusion were identical to those previously mentioned.

Immediately adjacent duplicate transmural samples of the left ventricular free wall were cut from the center of the area clearly discolored by ischemia and also from an area unaffected by ligation of the blood vessel. Samples were prepared for analysis of regional microsphere distribution and for microspectrophotometric analysis as described (24). Briefly, 30 μ m-thick frozen tissue sections were cut on a cold rotary microtome in a $-25^\circ C$ cold box in an N_2 atmosphere. Each section was then transferred to a precooled slide, covered with degassed silicone oil, and rapidly transferred to the microspectrophotometer cold stage flushed with N_2 gas.

¹ Abbreviation used in this paper: LAD: left anterior descending coronary artery.

Arteries and veins, 20–150 μ m in diameter, were located in the regions of interest and absorbances at 560, 523, and 506 nm were obtained to give O_2 saturation of the blood contained within the vessels. Only vessels seen in transverse sections were studied, so that the light path was only through blood. Between 7 and 10 arteries and 7 and 10 veins in the subepicardial and subendocardial regions of the occluded and unoccluded regions were observed. The adjacent tissue samples were prepared for blood flow determination. Blood flow was determined in milliliters per minute per 100 g (25).

Regional oxygen extraction (milliliters O_2 /100 ml blood) was calculated in the unoccluded area as the local arteriovenous differences multiplied by the arterial hemoglobin concentration times the maximal O_2 combining capacity of 1.36 ml O_2 /gram hemoglobin. Oxygen extraction for the occluded region was obtained from the unoccluded regional arterial O_2 saturation less the occluded regional venous O_2 saturation. Using the Fick principle, the oxygen consumption (MVO_2) for the regions of interest was determined as the product of O_2 extraction and regional blood flow (24). The ratio of O_2 supply to consumption was determined for each region studied.

Factorial analysis of variance was used to determine differences in hemodynamic parameters and blood gases before and after LAD occlusion and between treatments. A similar analysis of variance with repeated measures was used to determine differences between untreated and propranolol groups, unoccluded and occluded regions, and subepicardial and subendocardial regions, with respect to arterial and venous O_2 saturations, O_2 extraction, blood flow, O_2 consumption, and O_2 supply/consumption ratio. Sources of regional differences were determined by Duncan's multiple range test. Comparisons of small vessel O_2 saturation heterogeneities were made by use of the variance ratio test ("F" max). Differences between proportions of O_2 saturation distributions below a given saturation were determined by chi-square analysis (26). A value of $P < 0.05$ was considered significant.

RESULTS

The hemodynamic data are presented in Table I. Although initial transient depressions in aortic pressure and dP/dt frequently occurred after coronary occlusion, in every preparation there was a return to control levels before 10 min of occlusion. The untreated group showed no significant differences in any of the measured parameters after 2 h of LAD occlusion. A decrease in heart rate was found in the propranolol group. Heart rate and ventricular systolic pressure in this group were significantly reduced relative to the untreated group after occlusion. Left ventricular dP/dt was significantly greater in the propranolol-treated group during the control period than the untreated group. Mean dP/dt after occlusion and propranolol was lower ($P = 0.06$) than during the control period.

Aortic and coronary sinus blood gas and pH values were unaffected by LAD occlusion in the untreated group (Table II). The same was true for the group administered propranolol. Coronary sinus PCO_2 was lower in the propranolol group than the untreated group under control conditions.

TABLE I
Hemodynamic Data

	Preoccluded	Occluded
Heart rate, <i>beats/min</i>		
Untreated	168±36	178±23
Propranolol	165±22	143±18*†
Ventricular pressure, <i>mm Hg</i>		
Untreated	140±40/1.4±2.2	140±43/2.5±3.0
Propranolol	109±14/3.1±2.5	89±27‡/4.4±3.7
Aortic pressure, <i>mm Hg</i>		
Untreated	130±21/102±15	128±22/98±13
Propranolol	116±18/93±14	106±22/81±19
dP/dt, <i>mm Hg/s</i>		
Untreated	2,200±752	1,894±500
Propranolol	3,106±871§	2,177±957

* Significant change from value before occlusion (0.05).

† Propranolol occluded significantly different from untreated occluded group (0.05).

§ Propranolol control significantly different from untreated control (0.05).

Hemodynamic data: Values are before and 2 h after coronary occlusion in the presence (*n* = 8) and absence (*n* = 8) of propranolol 10 min after LAD ligation.

Regional arterial and venous O₂ saturations and O₂ extraction. 2 h of LAD occlusion brought about a significant decrease in arterial O₂ saturation within the

TABLE II
Blood Gas and pH Data

	Preoccluded	Occluded
Aortic blood samples		
PO ₂ , <i>mm Hg</i>		
Untreated	60±2	62±15
Propranolol	72±28	65±8
PCO ₂ , <i>mm Hg</i>		
Untreated	35±6	33±5
Propranolol	30±5	30±5
pH		
Untreated	7.42±0.08	7.43±0.05
Propranolol	7.41±0.05	7.43±0.06
Coronary sinus samples		
PO ₂ , <i>mm Hg</i>		
Untreated	20±2	20±1
Propranolol	22±6	21±7
PCO ₂ , <i>mm Hg</i>		
Untreated	48±6	46±5
Propranolol	40±7*	41±7
pH		
Untreated	7.36±0.09	7.37±0.08
Propranolol	7.39±0.04	7.37±0.06

* Propranolol control significantly different from untreated control (0.05).

Blood gas and pH data: Values are before and 2 h after coronary occlusion in the presence (*n* = 8) and absence (*n* = 8) of propranolol 10 min after LAD ligation.

affected myocardium of the untreated group. Mean O₂ saturation of the unoccluded and occluded regions was 94.1±5.7 and 82.8±17.5% (mean±total SD for all examined vessels), respectively. Propranolol treatment after LAD occlusion resulted in a significantly higher occluded O₂ saturation of 89.0±7.3%, which was not different from the propranolol-treated unoccluded region. The distribution of arterial O₂ saturations is shown in Fig. 1. Because there were no significant subepicardial-subendocardial differences, data from both were pooled. Note that the untreated arterial O₂ saturations in the occluded region show substantial variability with 38% of the vessels having O₂ saturations <80%. Propranolol significantly reduced the proportion of arteries with low O₂ saturation such that only 11% of them had saturations <80% (*P* < 0.001).

Venous saturations were similarly affected by occlusion in the untreated group. Mean unoccluded venous O₂ saturation was 37.6% (18.7% total SD, 5.7% between animal SD) while the occluded value was 25.2% (18.5% total SD, 4.1% between animal SD). This difference was significant. No significant transmural differences were found. Both subepicardial and subendocardial venous O₂ saturations in the unoccluded and the occluded regions were higher in the group treated with propranolol. The occluded venous saturations were significantly lower than those of the unoccluded region, 44.0% (6.2% total SD, 2.7% between animal SD) vs. 50.0% (7.5% total SD, 3.9% between animal SD), yet the effect was less pronounced than in the untreated group. Subendocardial O₂ saturations were significantly less than subepicardial O₂ saturations with propranolol. The distribution of venous O₂

FIGURE 1 Arterial O_2 saturation histograms (2 h postligation). Saturations of small arteries from subendocardial and subepicardial regions have been pooled. Panels A and B show the number of arteries with appropriate O_2 saturations in the unoccluded region of the untreated group and the group given propranolol 10 min after LAD ligation, respectively. Panels C and D provide the same data in the occluded region of the untreated and propranolol groups, respectively.

FIGURE 2 Regional venous O_2 saturation histograms (2 h postligation). The upper set of panels shows regional venous O_2 saturations in the untreated control occlusion group. The lower set provides values for the group treated with propranolol 10 min after LAD ligation. Panels A depict values from the nonoccluded subepicardium of each group, whereas panels B show unoccluded subendocardial venous saturations. Data in panel sets C and D are of subepicardial and subendocardial regions, respectively, in the occluded segments of each group.

saturations is given in Fig. 2. Note that occlusion brought about a predominance of veins with lower O_2 saturations transmurally in the untreated group, while propranolol strikingly eliminated the majority of these vessels, leading to a significantly smaller proportion having saturations below both 30 and 40% ($P < 0.001$).

O_2 extraction averaged 11.2 ± 2.5 ml O_2 /100 ml blood in the unoccluded region of the untreated group while extraction was significantly higher in the ischemic region at 13.8 ± 2.8 ml O_2 /100 ml of blood (Fig. 3). Propranolol reduced O_2 extraction in both regions transmurally. O_2 extraction remained elevated in the occluded region relative to the unoccluded region (7.8 ± 1.5 vs. 6.9 ± 1.9 ml O_2 /ml blood) with propranolol, yet the difference in O_2 extraction with occlusion was significantly less after propranolol treatment. Also, overall subendocardial O_2 extraction was significantly greater than subepicardial O_2 extraction (7.7 vs. 7.0 ml O_2 /100 ml blood) in this group.

Myocardial blood flow. Mean transmural blood flow (Fig. 4) in the untreated group was significantly lower in the center of the region made ischemic by LAD ligation (29.6 ± 38.5 ml/min per 100 g) than the unoccluded region (103.1 ± 68.2 ml/min per 100 g). Transmural differences in flow were not significant in either region. There was, however, a decrease in the subendocardial-to-subepicardial flow ratio from 1.16 to 0.41 in occlusion. Propranolol had no significant effect on the flow to the occluded region of the myocardium relative to the untreated group. Similar to the

FIGURE 3 Regional O_2 extraction. White bars represent regional O_2 extraction ($CaO_2 - CvO_2$) in the untreated occluded group, whereas black bars depict O_2 extraction in the occlusion plus propranolol group. Subepicardial as well as unoccluded and occluded region designations are given at the bottom of the figure. Values are expressed as mean $\pm$ SD.

FIGURE 4 Regional myocardial blood flow. White bars designate mean microsphere blood flow values for the untreated occluded group, whereas black bars refer to the occlusion plus propranolol group. Regional designations of the myocardium within the groups are identical to Fig. 3.

untreated group, flow was significantly lower in the occluded region relative to the unaffected region in the group given propranolol (35.6 ± 31.1 vs. 69.3 ± 31.4 ml/min per 100 g). The decrement in flow with propranolol, however, was significantly less than the untreated group. No transmural gradient of flow existed under propranolol treatment. Within the occluded region, relative subendocardial flow may have been marginally improved with propranolol (endocardial/epicardial ratio of 0.57 vs. 0.41 untreated).

Myocardial O_2 consumption. The control region of myocardium in the untreated group had an O_2 consumption of 11.9 ± 9.11 ml O_2 /min per 100 g (Fig. 5). Occlusion of the LAD caused O_2 consumption in the affected region to drop to 4.1 ± 5.50 ml O_2 /min per 100 g. Subendocardial O_2 consumption was somewhat higher than that of the subepicardium in the unoccluded region (13.2 ± 10.6 vs. 10.5 ± 7.8 ml O_2 /min per 100 g). This relationship was reversed in the occluded region, where subepicardial O_2 consumption was greater (5.9 ± 6.23 vs. 2.2 ± 4.26 ml O_2 /min per 100 g). The subendocardial-to-subepicardial ratio of O_2 consumption was significantly lower in the occluded compared with the control region. Propranolol decreased O_2 consumption in the unoccluded region. Transmural O_2 consumption in the propranolol group was significantly reduced in the ischemic region (2.8 ± 2.53 ml O_2 /min per 100 g) relative to the unaffected region (4.9 ± 2.9 ml O_2 /min per 100 g). The decrease in MVO_2 with occlusion was significantly less in the propranolol

FIGURE 5 Regional myocardial O_2 consumption. Regional O_2 consumption in the untreated occluded group is denoted by white bars, whereas the occlusion plus propranolol group is represented by black bars. The regional format is the same as in Fig. 3.

group than the untreated group. This was due to a lower unoccluded propranolol $M\dot{V}O_2$ relative to the untreated group (4.9 vs. 11.9 ml O_2 /min per 100 g) and no significant differences between groups in the occluded regions.

O_2 Supply/consumption ratio. The calculated O_2 supply-to-consumption ratio was significantly reduced by occlusion in the untreated group (Fig. 6). Propranolol increased this parameter significantly in the unoccluded region of the left ventricle. The reduction of O_2 supply relative to consumption caused by occlusion under control conditions was also evident after propranolol treatment. Within the center of the ischemic zone, however, transmural supply-to-consumption was significantly improved in the propranolol group relative to the untreated group (1.99 ± 0.14 vs. 1.45 ± 0.11).

DISCUSSION

The accuracy and limitations of the method used to determine regional O_2 consumption has been described in detail previously (22–24). Briefly, the accuracy of our determination of O_2 consumption depends on the accuracy of the determination of arterial and venous O_2 content and blood flow as well as the limitations of the Fick principle itself. The accuracy of microspectrophotometric determination of arterial

and venous O_2 saturation is $\sim \pm 3\%$. We have reported that we can freeze the heart quickly enough that no changes in O_2 saturation occur. We have recently measured O_2 saturations of arteries and veins within 1 mm of the subepicardial surface over time to determine the course of saturation changes in hearts stored at -70°C . Venous saturations were stable for 2 wk and arterial saturations for 4 wk. All hearts in our study were analyzed within 1 wk. The limitations of the radioactive microsphere method are well known. The accuracy of our determination of regional consumption is better than $\pm 9\%$ compared with standard techniques.

Although coronary artery occlusion causes alterations in regional contractility (1), metabolism (2, 3), and the microvasculature (4, 5), these changes are in part dependent upon the extent to which the balance between O_2 supply and demand has been impaired. Occlusion decreases blood flow to the myocardium supplied by the artery in question and results in a disproportionate diminution of flow to the deeper sub-endocardium (17, 18).

Propranolol has been shown to reduce the extent of myocardial necrosis following coronary artery occlusion (12, 27), yet the mechanism of its beneficial effects remains unclear. The blood flow response to propran-

FIGURE 6 Regional O_2 supply/consumption ratio. Regional O_2 supply/consumption ratio or $SaO_2/(SaO_2 - SvO_2)$ for the untreated occlusion group are found in the white bars, whereas the black bars represent this relationship in the propranolol group. The regional designations found in Fig. 3 are used here.

olol in the ischemic region has not been consistent in previous studies. Kloner et al. (28) found ischemic flow to decrease with propranolol and Melby and Bache (20) found no change in absolute flow or transmural distribution in the anesthetized dog. Vatner et al. (18) showed that ischemic flow increased significantly with propranolol in the conscious dog. Still others found substantial changes in the transmural distribution of blood flow, favoring the subendocardium (17, 29). Although the negative inotropic effect of propranolol has been emphasized (29) it is still not certain what role it plays, if any, in the drug's effect on ischemic myocardium. The purpose of this study, therefore, was to investigate various parameters of the O₂ supply/consumption ratio in the occluded coronary artery preparation treated with propranolol and to relate this data to possible mechanisms of action of the drug.

Coronary occlusion brought about no significant changes in the measured hemodynamic or blood gas and pH parameters measured, in agreement with previous studies (11, 19). Occlusion plus propranolol treatment caused heart rate, dP/dt, and left ventricular systolic pressure to decrease due to blockade of β_1 -adrenergic receptors. Neither aortic peak systolic nor end diastolic pressures were significantly affected by occlusion plus the drug.

Coronary artery ligation was accompanied by a significant decrease in blood flow to the region of the left ventricle supplied by the LAD. The decrease in subendocardial/subepicardial flow ratio in the ischemic area was expected from other studies (11, 17, 18, 20). Propranolol, in our preparation, neither significantly altered the magnitude of flow nor the subendocardial/subepicardial ratio of ischemic blood flow relative to the untreated group.

The distribution of arterial saturations within the center of the untreated unoccluded region showed only 2% of the vessels with saturations <80%. Occlusion increased this proportion of vessels to 38%. Similar values have been found (11). Previous results with this technique have shown that loss of perfusion pressure due to fibrillation for a period of 2 min results in no change in the O₂ saturation of small arteries in the dog heart (23). Therefore, the lowered arterial O₂ saturations found in the ischemic region must be indicative of vessels with extremely low or no flow after 2 h of coronary artery ligation. Steenbergen et al. (30) and Chance et al. (31) have also shown heterogeneous O₂ delivery to the cellular cytochrome chain in the hypoxic heart. Propranolol significantly reduced the proportion of arteries within the occluded region having O₂ saturations <80%. Because there are very few arteries with low O₂ saturations found within the occluded region after propranolol, there must be a vessel-by-vessel redistribution of flow, perhaps caused by

direct vascular or indirect local metabolic alterations. It should be noted that this redistribution occurs in the absence of a significant increase in volume or change in transmural distribution of ischemic flow, according to the microsphere technique.

A more striking effect of propranolol was seen in the venous O₂ saturation. While occlusion significantly reduced the mean venous O₂ saturation and skewed the distribution of saturations toward the low end, propranolol completely eliminated this effect. Not only was the distribution of venous saturations more uniform after propranolol (note lower total SD values), but it was at a much higher level of O₂ saturation. That this phenomenon exists in the occluded and unoccluded regions shows that extraction has become more uniform and decreased throughout the heart. This was confirmed when regional O₂ extraction was computed. A global decrease in O₂ extraction and an increase in uniformity of O₂ extraction was evident. Even though ischemic O₂ extraction was greater than normal tissue with propranolol, the extent of this difference was significantly less than in untreated dogs.

Occlusion caused O₂ consumption to drop in both groups because the decrement in flow was greater than the increase in extraction. Within the ischemic region, neither the average subepicardial nor subendocardial $\dot{M}\dot{V}O_2$ was significantly different in comparisons between control and propranolol-treated groups.

The β_1 -adrenergic blocking effect of propranolol clearly causes a decreased chronotropic and inotropic effect and a resultant decrease in $\dot{M}\dot{V}O_2$ in the unoccluded region of the heart. These effects have been suggested to promote a transmural redistribution of blood flow within the ischemic zone that is a primary determinant of the beneficial effect of the drug (29, 32). It is unlikely that this tells the entire story because Berdeaux et al. (33) and Warltier et al. (27) have used pharmacological agents lacking β -adrenergic blocking activity that do decrease the chronotropic and inotropic state of the heart without causing a redistribution of ischemic flow or decreasing eventual infarct size in these respective studies. Further, there are studies including the present one in which propranolol does not redistribute flow within the ischemic zone.

It might be argued that redistribution of arterial flow after propranolol promotes a more uniform capillary and venous flow, thereby causing venous O₂ saturations to be more homogeneous. This explanation is unlikely for a number of reasons. First, the variability of arterial O₂ saturations in unoccluded and occluded regions after propranolol are similar to control conditions (23). The veins with low O₂ saturations under control conditions are not, however, present after propranolol treatment. Secondly, such an argument would suggest a significant heterogeneity and high level of

β_2 -adrenergic receptor activity within the ischemic region of myocardium that is abolished by propranolol administration. We know of no evidence that supports this hypothesis. If flow is not the sole cause of more uniform venous O_2 saturations, then O_2 consumption and O_2 extraction must play an important role.

We hypothesize that there is a microregional difference in distribution and/or activity of β_1 -adrenergic receptors. There is evidence that myocardial β -adrenergic receptor binding differs regionally (34), although this has not been studied on a microregional basis. Areas of higher number or activity would have higher O_2 consumptions and this may explain the heterogeneity of myocardial venous O_2 saturations in normal heart (23). It has been suggested that coronary artery occlusion promotes increased circulating (35) and local myocardial (36) catecholamines. This could explain the marked heterogeneity of arterial and venous O_2 saturation seen in an ischemic zone (11). The effect of propranolol in myocardial ischemia would be to reduce the tone and hence O_2 consumption of these microregions of high β -adrenergic activity. Mueller and Ayres (37) have also postulated a decreased sympathetic nerve activity with propranolol administration in myocardial infarction. This effect of propranolol could redistribute blood flow and reduce differences in arterial and venous O_2 saturations in ischemia through this homogenization of microregional O_2 consumption. This could explain the improvement in ST segment elevation in the face of an overall decrease in ischemic flow with propranolol (38). While nonspecific effects of propranolol such as reduction of microvascular damage and blood stasis (15) cannot be ruled out in explaining some of the improvement in O_2 saturations in the ischemic region, it is doubtful that they can be applied to similar results seen in the normal myocardium. A reduction in the heterogeneity of β_1 -adrenergic activity with propranolol would also explain the improvement in the O_2 supply to consumption ratio throughout the normal and ischemic regions of the heart.

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