Changes in Ischemic Blood Flow Distribution and Dynamic Severity of a Coronary Stenosis Induced by Beta Blockade in the Canine Heart

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SUMMARY The effects of equipotent β-receptor-blocking doses of propranolol, metoprolol and sotalol on distal coronary pressure, stenosis resistance and regional myocardial blood flow (endo/epi) were studied in anesthetized dogs with a severe noncircumferential stenosis of the left circumflex coronary artery. No significant differences between the three β blockers were observed for overall hemodynamics and regional myocardial blood flow. After drug treatment, subendocardial blood flow (0.47 ± 0.05 to 0.78 ± 0.05 ml/min/g) and endo/epi (0.67 ± 0.04 to 1.18 ± 0.04) increased significantly (p < 0.05) in the ischemic region. These changes were associated with a marked increase in distal coronary perfusion pressure and a decrease in heart rate. Resistance across the stenosis decreased significantly (p < 0.05) after β-receptor blockade (3.2 ± 0.3 to 1.4 ± 0.2 units). Atrial pacing to control heart rate only partially attenuated these changes. These results suggest that a favorable redistribution of ischemic blood flow after β blockade is the result of an increase in distal diastolic pressure-time index and an autoregulation-induced increase in distal bed vascular resistance due to a decrease in myocardial oxygen demand associated with β blockade. The latter effect also resulted in a decrease in the dynamic severity of a proximal coronary stenosis.

BETA-ADRENERGIC-RECEPTOR antagonists effectively alleviate the symptoms of angina pectoris. How these agents reduce myocardial ischemia, however, is controversial. Most investigators favor the concept that β-receptor antagonists reduce ischemia by decreasing myocardial oxygen demands through negative inotropic and chronotropic actions, but an increase in oxygen supply caused by enhanced blood flow to ischemic areas may also be an important factor. Beta antagonists produce a redistribution of blood flow from subepicardium to subendocardium in nonischemic and acutely ischemic dog hearts. The non-β-blocking properties of these drugs, such as intrinsic sympathomimetic or membrane-stabilizing activity, do not appear to influence their ability to redistribute tissue blood flow. However, Berdeaux et al. suggested that a simultaneous β- and β-receptor blockade might be necessary for flow redistribution. In contrast, Marshall and Parratt suggested an advantage of cardioselective β blockade on ischemic blood flow, while Buck et al. showed that both cardioselective and noncardioselective agents could favorably influence the ischemic endocardial-epicardial flow (endo/epi) ratio.

Walinsky et al. demonstrated that changing resistance across a fixed proximal coronary stenosis is critical in determining the quality of flow to ischemic myocardium. Schwartz et al. described a dependence of stenotic resistance on distal coronary perfusion pressure in the intact dog heart, a finding supported by previous in vitro investigations. Since then, Santamore and Walinsky found that interventions that lower coronary arterial pressure distal to a stenosis increase stenotic resistance and, paradoxically, may decrease total coronary blood flow, whereas interventions that increase distal pressure may act to decrease stenotic resistance to flow. An interaction between stenosis and distal bed coronary resistances ultimately determined whether a vasactive agent increased or decreased coronary blood flow. According to Santamore and Walinsky, a reduction in coronary perfusion pressure would lead to a maldistribution of myocardial blood flow and an increase in subendocardial ischemia or, conversely, an elevation of perfusion pressure would lead to a decrease in subendocardial ischemia. The effect of β blockade on distal coronary pressure and transmural blood flow has not been studied experimentally. Therefore, this study was designed to determine the relative effect of three β-receptor antagonists, propranolol, sotalol and metoprolol, on total ischemic myocardial blood flow and its transmural distribution (endo/epi ratio). The relationships between transmural flow distribution and changes in distal coronary perfusion pressure and stenosis resistance or cardioselective vs nonselective β-receptor blockade were also examined.

Methods

Experimental Preparation

Adult mongrel dogs of either sex that weighed 15–25 kg were fasted overnight, anesthetized with i.v. sodium pentobarbital (30 mg/kg) and ventilated by a respirator (Harvard Model 607) with room air at 10–15 breaths/min. Atelectasis was prevented by maintaining an expiratory pressure of 5–7 cm of water with a trap. Body temperature was maintained at 38 ± 1°C by a heating pad and servomechanical controller.
Arterial blood pressure was recorded by means of a catheter inserted into the right femoral artery, advanced to the thoracic aorta and attached to a strain-gauge pressure transducer (Statham P23Db). The right femoral vein was catheterized for drug administration and the left femoral artery was catheterized for withdrawal of reference arterial blood samples used in determining regional myocardial blood flow. Left ventricular systolic and end-diastolic pressures were recorded by means of a pressure-transducer-tipped catheter (Millar PC380, #8F) passed through the left carotid artery into the left ventricle. The transducer was zeroed at atmospheric pressure and calibrated with a mercury manometer. The first derivative of left ventricular pressure (dP/dt) was obtained by electronic differentiation of the left ventricular pressure pulse.

Thoracotomy was performed at the left fifth intercostal space, the lung was gently retracted and the heart was suspended in a pericardial cradle. A 1–1.5-cm segment of the left circumflex coronary artery was dissected from surrounding tissue near its origin, and a calibrated flow probe (Statham SP7515) was placed around the vessel. Coronary blood flow was recorded by use of an electromagnetic flowmeter (Statham 2202). A micrometer-driven mechanical vessel occluder was placed distal to the probe so that no branches were present between the probe and occluder. Constriction of the vessel was accomplished by compressing the vessel between a hook-shaped stainless steel plate and a chromel plunger covered with silicone rubber and bent to fit the pressure plate. A micrometer moved the occluder head in 0.01-mm units by means of a drive lever that could be manually depressed to occlude the vessel completely. The occluder was used to determine zero blood flow and to produce a noncircumferential coronary artery stenosis of a constant 3-mm length. Distal coronary perfusion pressure was obtained by cannulating (PE 90 tubing) the first major branch of the left circumflex coronary artery distal to the stenosis and attaching the cannula to a pressure transducer (Statham P23Db). A catheter was placed in the left atrium via the atrial appendage for injection of tracer microspheres.

Myocardial contractile force of the tissue perfused by the left anterior descending coronary artery was determined by a Walton-Brodie strain gauge arch. The gauge was attached to the left ventricular free wall and oriented perpendicular to the base-apex axis of the heart. The gauge was stretched to approximately 140% of its initial diastolic length. Changes in myocardial contractile force were expressed as percentage of control.

To prevent platelet aggregation, the dogs were treated with i.v. aspirin (30 mg/kg) before application of the stenosis. Intravenous heparin, 500 U/kg, was also administered. The ECG (limb lead II), phasic and mean aortic blood pressure, left ventricular systolic and end-diastolic pressures, dP/dt, phasic and mean coronary perfusion pressure, myocardial contractile force and phasic and mean coronary blood flow were continuously recorded on a polygraph (Grass 7).

Regional Myocardial Blood Flow

The distribution of coronary blood flow was determined by using the radioactive microsphere technique. Carbonized plastic microspheres (15 ± 3 μm diameter, 3M Company) labeled with 141Ce, 85Sr, 51Cr, and 54Sc were obtained as 2 mCi of nuclide in 10 ml of isotonic saline, to which 1 drop of Tween 80 was added to minimize aggregation. The mixture was agitated before injection in a vortex mixer (Cole-Parmer 4722) for 15 minutes. Approximately 2–4 × 10⁶ microspheres were injected into the left atrium in a total volume of 0.75–1.0 ml, followed by an 8-ml saline (37°C) wash. A few seconds before each microsphere injection, a timed collection of reference flow from the femoral artery was started and maintained at a constant rate (7 ml/min) for 3 minutes.

Experimental Design

To determine equipotent β₁-receptor blocking doses, the effectiveness of each drug in antagonizing the chronotropic responses to various doses of i.v. isoproterenol (0.03–30 μg/kg) was tested in an initial three series of six nonischemic animals. The dose that produced a 10-fold shift to the right in the chronotropic dose-response curve to isoproterenol was 0.2 mg/kg for propranolol, 0.3 mg/kg for metoprolol and 1.0 mg/kg for sotalol. These relative potencies compare favorably with previously reported values.

In the ischemia series, the preparation was allowed to stabilize for 30 minutes after surgery. Three experimental groups (propranolol, metoprolol and sotalol) of six dogs each were completed. An additional control group of four dogs received saline solution. In each group, a stenosis of the left circumflex coronary artery sufficient to reduce resting coronary blood flow and distal coronary arterial pressure in the ischemic region 40–50% was produced by the mechanical occluder. Another 30-minute stabilization period was then allowed. In each group, microspheres were injected during a control period, 30 minutes after i.v. administration of either saline, propranolol, metoprolol or sotalol, after aortic pressure was corrected by administering methoxamine, if needed (100–300 μg, n = 4), and after heart rate (by means of atrial pacing) was corrected to predrug levels.

Analysis of Left Ventricular Tissue Samples

After completion of the experiment, the left circumflex coronary artery was ligated, and 1 ml of India ink was injected distal to the ligation at the mean arterial blood pressure of the dog to darken the area of myocardium subjected to stenosis. The heart was excised, washed with saline and fixed in 10% formalin for 24 hours. The left ventricle was sectioned into base, middle and apex of both anterior (area perfused by the left anterior descending artery) and posterior (area perfused by the left circumflex artery) regions. These
samples were subdivided into subepicardial (outer) and subendocardial (inner) layers of approximately equal weight (2–3 g). All tissue samples were weighed and placed in glass scintillation vials, and the activity of the isotopes in each tissue sample was determined at four energy windows in an autogamma spectrometer (Searle Analytic 1195). The activity of each isotope in the reference blood flow sample was determined in a similar manner. Myocardial blood flow in the tissue samples was calculated as described elsewhere. The tissue areas of the base, middle and apex were pooled for calculation of blood flow in the subepicardium and subendocardium of the nonischemic and ischemic regions. Transmural blood flow was the weighted average obtained from the subepicardium and subendocardium of the nonischemic or ischemic region of each heart.

Calculation of Indexes

The tension-time index (TTI) was calculated by determining the area under the aortic systolic blood pressure curve and multiplying by heart rate. The distal diastolic pressure-time index (DDPTI) was calculated by determining the area between the distal diastolic coronary artery and left ventricular end-diastolic pressure curves and multiplying by heart rate. The ratio of DDPTI/TTI was used as an approximate index of ischemic myocardial oxygen balance. Both indexes suffer from limitations; i.e., TTI does not account for changes in myocardial contractility and DDPTI may overestimate the potential for subendocardial perfusion. Resistance across the stenosis was calculated by dividing the difference between the diastolic aortic and distal diastolic coronary arterial pressures by diastolic coronary blood flow at end-diastole, as suggested by Gould. Distal coronary vascular resistance was calculated by dividing the diastolic peripheral coronary arterial pressure by diastolic coronary blood flow at end-diastole.

Data Analysis

Transmural distribution of coronary blood flow was expressed as the ratio of counts per gram subendocardium to counts per gram subepicardium (endo/epi ratio). Tissue blood flow was expressed in ml/min/g. Statistical analysis between groups was made by analysis of variance. Individual comparisons between control, β blockade and β blockade plus pacing were performed by use of the Newman-Kuels test. Linear regression analysis was also used to determine correlations between certain hemodynamic variables. Differences between endo/epi ratios and hemodynamic data were considered significant when \( p < 0.05 \). Values are mean ± SEM.

Results

Control Series

Adjustments in the level of coronary blood flow by the occluder were necessary to reach a stable state during the first 30 minutes of left circumflex coronary arterial stenosis. In four dogs treated with saline, no significant changes in hemodynamics and ischemic transmural blood flow (endo/epi ratio, 0.64 ± 0.07 to 0.66 ± 0.06) occurred between 30 and 60 minutes, which indicates the stability of the stenosis during this time. These results are in agreement with previous data from this laboratory.

Hemodynamic Effects

Table 1 is a summary of the individual and combined effects of propranolol (0.2 mg/kg), metoprolol (0.3 mg/kg) and sotalol (1.0 mg/kg) on coronary blood flow and systemic hemodynamics. All three blockers produced similar qualitative and quantitative changes (no significant differences by analysis of variance) and are treated as a single group in the following discussion. These data further indicate that a similar degree of β blockade was produced by each agent at the chosen dose.

Beta-adrenergic blockade produced a significant \( (p < 0.05) \) decrease in heart rate, dP/dt and myocardial contractile force. After heart rate was returned to predrug levels by atrial pacing, contractile force and dP/dt still remained significantly reduced.

Distal Coronary Pressures

Systolic, diastolic and mean distal coronary perfusion pressures were significantly increased after β-receptor blockade (table 2). In addition, the difference between the diastolic peripheral coronary pressure (DPCP) and left ventricular end-diastolic pressure (LVEDP) at end-diastole, an estimate of the perfusion pressure gradient for blood flows in different layers of the ischemic region, was also significantly increased after β blockade. DDPTI was also increased, which resulted in a significant improvement in the ischemic subendocardial oxygen supply-demand (DDPTI/TTI) balance. All distal pressures and calculated indexes remained significantly increased from control despite atrial pacing. On the other hand, pacing significantly decreased DDPTI and DDPTI/TTI from values obtained during β blockade; however, distal pressures were not significantly lower during pacing (table 2).

Stenosis and Distal Coronary Resistance

Resistance to flow through the stenosis decreased significantly after β blockade (fig. 1), whereas distal coronary resistance increased. Pacing the heart back to control did not significantly alter the effects of β blockade on calculated stenosis and distal resistances.

Regional Myocardial Blood Flow

Beta-adrenergic blockade produced a significant decrease in blood flow to all layers of nonischemic myocardium (table 3). No change in endo/epi ratio occurred. Atrial pacing returned transmural flow to control. In contrast, β blockade produced a significant increase in subendocardial blood flow and endo/epi ratio in the ischemic region (table 3). Subepicardial
and transmural flow did not change. Subendocardial blood flow remained significantly elevated from control and was not different from that with β blockade despite atrial pacing. The endo/epi ratio in the ischemic region remained significantly elevated from control during atrial pacing, but it was decreased from that with β blockade alone.

**Discussion**

The dog model developed to produce regional myocardial ischemia differs from others in which β-adrenergic blocking agents were studied after total coronary artery occlusion, but resembles that of Tomoike et al., who studied the effect of propranolol in a partial coronary occlusion model in conscious dogs. In the present model, distal coronary pressures, stenosis and distal resistances and regional myocardial blood flow were measured so that potential mechanisms by which β-adrenergic antagonists attenuate ischemia could be determined. The stability of this model of ischemia in the absence of drug treatment has been shown in the present study and other studies from this laboratory.

**Myocardial Blood Flow Redistribution After Nonselective or Cardioslective β-receptor Blockade**

This study indicates that nonselective β1- and β2-receptor blockade induced by propranolol and sotalol or cardioslective β1-receptor blockade induced by metoprolol results in a favorable redistribution of blood flow in an ischemic region of the myocardium. This increase in blood flow and oxygen supply (as expressed by the DDPTI) plus an overall decrease in myocardial oxygen demand (due to decreases in heart rate, dP/dt and myocardial contractility) produced by β blockade result in an improvement in oxygen balance of the ischemic myocardium.

**Mechanisms Involved in Redistribution of Ischemic Blood Flow**

Results of a recent study suggest that blockade of β2 vascular receptors by propranolol and pindolol

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**Table 1. Comparative Hemodynamic Effects of Propranolol (n = 6), Metoprolol (n = 6) and Sotalol (n = 6) During Stenosis of the Left Circumflex Coronary Artery**

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>MAP (mm Hg)</th>
<th>dP/dt (mm Hg/sec)</th>
<th>MCBF (ml/min)</th>
<th>CF (% control)</th>
<th>TTI (mm Hg/sec/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>161 ± 10</td>
<td>100 ± 4</td>
<td>1941 ± 308</td>
<td>20 ± 2</td>
<td>100</td>
<td>3091 ± 178</td>
</tr>
<tr>
<td>Propranolol</td>
<td>128 ± 8*</td>
<td>103 ± 3</td>
<td>1616 ± 234*</td>
<td>22 ± 2</td>
<td>59 ± 9*</td>
<td>2796 ± 190</td>
</tr>
<tr>
<td>Propranolol and pacing</td>
<td>161 ± 10</td>
<td>99 ± 3</td>
<td>1500 ± 152*</td>
<td>20 ± 2</td>
<td>69 ± 16*</td>
<td>2946 ± 216</td>
</tr>
<tr>
<td>Control</td>
<td>164 ± 7</td>
<td>108 ± 4</td>
<td>2091 ± 182</td>
<td>21 ± 1</td>
<td>100</td>
<td>3229 ± 198</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>127 ± 5*</td>
<td>108 ± 4</td>
<td>1616 ± 153*</td>
<td>32 ± 4</td>
<td>58 ± 12*</td>
<td>3077 ± 160</td>
</tr>
<tr>
<td>Metoprolol and pacing</td>
<td>164 ± 7</td>
<td>109 ± 4</td>
<td>1741 ± 156</td>
<td>33 ± 5</td>
<td>64 ± 9*</td>
<td>3259 ± 177</td>
</tr>
<tr>
<td>Control</td>
<td>156 ± 11</td>
<td>115 ± 10</td>
<td>2316 ± 228</td>
<td>30 ± 4</td>
<td>100</td>
<td>3555 ± 369</td>
</tr>
<tr>
<td>Sotalol</td>
<td>118 ± 6*</td>
<td>117 ± 11</td>
<td>1800 ± 154*</td>
<td>32 ± 3</td>
<td>65 ± 6*</td>
<td>3165 ± 321</td>
</tr>
<tr>
<td>Sotalol and pacing</td>
<td>156 ± 10</td>
<td>115 ± 9</td>
<td>1950 ± 179</td>
<td>26 ± 3</td>
<td>68 ± 6*</td>
<td>3611 ± 328</td>
</tr>
<tr>
<td>Control</td>
<td>160 ± 5</td>
<td>107 ± 4</td>
<td>2116 ± 134</td>
<td>23 ± 2</td>
<td>100</td>
<td>3308 ± 145</td>
</tr>
<tr>
<td>β blockade</td>
<td>125 ± 6*</td>
<td>109 ± 4</td>
<td>1677 ± 102*</td>
<td>29 ± 2</td>
<td>60 ± 5*</td>
<td>3013 ± 132</td>
</tr>
<tr>
<td>β blockade and pacing</td>
<td>160 ± 5</td>
<td>107 ± 4</td>
<td>1730 ± 99*</td>
<td>26 ± 2</td>
<td>65 ± 7*</td>
<td>3272 ± 150</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
*p < 0.05 vs control.

Abbreviations: HR = heart rate; MAP = mean arterial pressure; MCBF = mean coronary blood flow (MCBF before stenosis in each group was as follows: propranolol, 40 ± 5 ml/min; metoprolol, 42 ± 5 ml/min; sotalol, 50 ± 8 ml/min; β blockade, 44 ± 4 ml/min); CF = contractile force; TTI = tension-time index.

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**Table 2. Effects of β Blockade on Distal Coronary Pressure During Stenosis of the Left Circumflex Coronary Artery**

<table>
<thead>
<tr>
<th></th>
<th>SPCP (mm Hg)</th>
<th>DPCP (mm Hg)</th>
<th>MPCP (mm Hg)</th>
<th>DPCP-LVEDP (mm Hg)</th>
<th>DDPTI (mm Hg/sec/min)</th>
<th>DDPTI/TTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>53 ± 4</td>
<td>32 ± 2</td>
<td>41 ± 3</td>
<td>24 ± 2</td>
<td>1143 ± 97</td>
<td>0.35 ± 0.03</td>
</tr>
<tr>
<td>β blockade</td>
<td>91 ± 6*</td>
<td>66 ± 6*</td>
<td>75 ± 6*</td>
<td>59 ± 5*</td>
<td>2376 ± 214*</td>
<td>0.78 ± 0.05*</td>
</tr>
<tr>
<td>β blockade and pacing</td>
<td>75 ± 6*</td>
<td>53 ± 6*</td>
<td>61 ± 6*</td>
<td>43 ± 6*</td>
<td>1808 ± 220*†</td>
<td>0.57 ± 0.06†</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 18).
*tp < 0.05 vs control.

Abbreviations: SPCP = systolic peripheral coronary pressure; DPCP = diastolic peripheral coronary pressure; MPCP = mean peripheral coronary pressure; LVEDP = left ventricular end-diastolic pressure; DDPTI = distal diastolic pressure-time index; TTI = tension-time index.
resulted in an "unmasking" of α-adrenergic vasoconstrictor receptors, which are abundant in subepicardial layers, to the effects of circulating catecholamines, which would result in an increase in vascular resistance in the subepicardium relative to the subendocardium, which has few α receptors.26 The larger increase in vascular resistance in subepicardium would redistribute blood flow toward the subendocardium, where vascular resistance is less. Pratolol and other cardioselective inhibitors, by leaving epicardial β₂ vasodilator receptors unblocked to counter α-receptor-mediated vasoconstriction, would not be expected to increase flow to the ischemic subendocardium.7 Buck et al., using a partial occlusion model, reported that two cardioselective compounds, bevantolol and pratolol, as well as propranolol, a nonselective agent, increased the ischemic endo/epi ratio. That finding and the present results indicate that the increased endo/epi ratio after β-receptor blockade is probably not associated with an unmasking of α-adrenergic receptors in the coronary bed.

An increase in diastolic perfusion time produced by β-blockade-induced bradycardia has been proposed to be critically important in restoring blood flow to ischemic subendocardium.28 Further, the effects of propranolol and pratolol on increasing flow to normal or ischemic areas of the canine myocardium have been shown to be partially abolished by atrial pacing.3 On the other hand, Gross and Winbury4 have shown that a reduction in heart rate produced by β blockade under conditions of maximal coronary vasodilatation did not result in an improvement in the endo/epi ratio. In addition, other investigators have failed to find a significant correlation between heart rate and an increased endo/epi ratio on ischemic blood flow.4,5 Recently, in work designed to assess the effect of propranolol on the ischemic myocardium via intramural myocardial carbon dioxide tension, Hillis et al.27 showed that propranolol exerts most of its effects independent of heart rate. The results of the present study also indicate that heart rate is not totally responsible for the beneficial actions of β blockade on ischemic myocardial blood flow distribution. Atrial pacing only partly returned ischemic endo/epi ratio to control.

Marshall and Parratt6 showed that propranolol reduced the ischemic transventricular driving pressure, possibly negating the beneficial effects of drug-induced bradycardia on improving subendocardial blood flow. Although this effect was thought to be primarily the result of an increased LVEDP or downstream pressure, which are not equivalent but usually change in the same direction,28 it does show the possibility that pressure changes in the ischemic vasculature independent of heart rate might be acting to redistribute flow after β blockade. Just as aortic diastolic pressure is an important determinant of myocardial oxygen supply in the absence of a stenosis, diastolic diastolic coronary pressure should be crucial in establishing the oxygen supply status of the ischemic bed.

**TABLE 3. Effects of μ Blockade on Normal and Ischemic Myocardial Blood Flow During Stenosis of the Left Circumflex Coronary Artery**

<table>
<thead>
<tr>
<th></th>
<th>Epicardium (ml/min/g)</th>
<th>Endocardium (ml/min/g)</th>
<th>Transmural (ml/min/g)</th>
<th>Endo/epi</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonischemic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.82 ± 0.04</td>
<td>0.99 ± 0.05</td>
<td>0.91 ± 0.05</td>
<td>1.19 ± 0.04</td>
</tr>
<tr>
<td>β blockade</td>
<td>0.69 ± 0.03*</td>
<td>0.78 ± 0.04*</td>
<td>0.75 ± 0.03*</td>
<td>1.17 ± 0.03</td>
</tr>
<tr>
<td>β blockade</td>
<td>0.79 ± 0.04†</td>
<td>0.90 ± 0.05*</td>
<td>0.85 ± 0.05†</td>
<td>1.11 ± 0.07</td>
</tr>
<tr>
<td>and pacing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ischemic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>0.76 ± 0.06</td>
<td>0.47 ± 0.05</td>
<td>0.63 ± 0.04</td>
<td>0.67 ± 0.04</td>
</tr>
<tr>
<td>β blockade</td>
<td>0.67 ± 0.04</td>
<td>0.78 ± 0.05*</td>
<td>0.72 ± 0.04</td>
<td>1.18 ± 0.04*</td>
</tr>
<tr>
<td>β blockade</td>
<td>0.74 ± 0.06</td>
<td>0.66 ± 0.07*</td>
<td>0.70 ± 0.07</td>
<td>0.84 ± 0.07†</td>
</tr>
<tr>
<td>and pacing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SEM (n = 18).

* p < 0.05 vs control.

† p < 0.05 vs β blockade.
myocardium in the presence of a stenosis. An increased transmural perfusion pressure, expressed as DCP - LVEDP, might theoretically parallel an increase in subendocardial blood flow, and the present results substantiate this experimentally (table 2).

If unmasking of $\alpha$ receptors is not responsible, another mechanism must be involved in the increase in the diastolic coronary perfusion pressure gradient observed after $\beta$ blockade. Gross and Winbury suggested that it may be due to the differential effects of a reduced myocardial oxygen consumption on resistance vessels of the subepicardium and subendocardium in ischemic areas. Because arteriolar dilator reserve in the subendocardium is likely to be absent during conditions of ischemia, when metabolism is slowed after $\beta$ blockade, coronary vascular resistance should increase primarily in the subepicardium. Because of this regional autoregulation a shift in blood flow to inner layers of less resistance would be expected to occur, and the ischemic endo/epi ratio would therefore increase. Alternatively, a differential sensitivity of subendocardial vs subepicardial vessels to $\beta$ blockade might also explain this favorable shift in flow to inner layers. In support of this hypothesis, Domenech and MacLellan recently presented evidence to suggest a greater number of $\beta_2$ vasodilator receptors in subepicardium than subendocardium. If this is the case, $\beta$-receptor blockade might be expected to shift flow to the subendocardium by blocking the predominance of vasodilator receptors in the subepicardium.

Beta-blockade-induced increases in endo/epi ratio were correlated ($r = 0.81, p < 0.001$) with DDPTI, which incorporates the effects of bradycardia and increased distal coronary pressure in the same index (fig. 2). Buckberg et al. found that when diastolic coronary blood flow is severely compromised by reduced perfusion pressure or by abbreviation of diastole, the decreased subendocardial blood flow and endo/epi ratio that results could be accurately predicted by the DPTI. Similarly, an index similar to DPTI has recently been shown by Munch and Downey to be accurate at predicting changes in subendocardial flow during maximal vasodilation or when a partial coronary occlusion was present. In the presence of a severe coronary stenosis, however, DPTI calculated from aortic rather than distal coronary pressure overestimates the oxygen supply to ischemic areas. Therefore, DDPTI was used in the present study to estimate the potential for subendocardial perfusion in the ischemic area. On the other hand, even the use of this index (DDPTI) to predict changes in subendocardial flow and the endo/epi ratio must be used with caution. Hoffman suggested that DPTI, or in our case DDPTI, may overestimate the potential for subendocardial blood flow because diastolic intramyocardial pressures may exceed LVEDP. Nevertheless, the mechanism for the increase in DDPTI and parallel increase in the ischemic endo/epi ratio is most likely due to a $\beta$-blockade-induced reduction in regional myocardial oxygen demand to the point where the available coronary blood flow becomes sufficient to meet tissue needs. The finding that transmural flows in non-ischemic and ischemic areas were nearly equal after $\beta$ blockade ($0.75 \pm 0.03$ vs $0.72 \pm 0.04$ ml/min/g) (table 3) supports this possibility. Restoration of the ability of the resistance vessels to autoregulate in the ischemic area resulted in an increase in distal resistance and distal coronary perfusion pressure.

**Changes in Stenosis Severity After $\beta$-receptor Blockade**

The results of this study also show that $\beta$-adrenergic blockade produces a decrease in the severity of a fixed proximal coronary artery stenosis (fig. 1). Resistance to flow through the stenosis site decreased significantly after drug administration and remained below control after atrial pacing.

Previous studies in open-chest animals have shown that calculated coronary artery stenosis resistance increases after distal vasodilation accompanying a reduction in distal arterial pressure. Renal arterial stenosis resistance has also been shown in intact dogs to be dependent on distal pressure and renal vascular bed resistance.

Gould suggested four mechanisms for altered severity of coronary arterial stenosis during changing vasomotor states of the distal vasculature: vasodilation of the artery adjacent to the stenosis segment; arterial smooth muscle relaxation and vasodilation of the stenotic segment itself; the appearance of fully developed turbulence in the stenotic segment; and narrowing of the stenotic segment due to decreasing intraluminal pressure after arteriolar vasodilation or expansion of the stenotic segment by increasing intraluminal pressure after arteriolar vasoconstriction. The latter mechanism is supported by recent evidence in the open-chest dog, where agents such as isoproter-
enol or nitroglycerin, which decreased distal coronary pressure, increased stenosis severity, whereas vasocostricators such as methoxamine and vasopressin, which increased distal pressure, decreased stenosis resistance. When the stenosis diameter was maintained with intraluminal plastic tubing, decreased distal coronary pressure did not influence stenosis resistance, presumably because the artery was rendered incapable of passive narrowing.

The present results also show the dependence of stenosis resistance on intraluminal distal coronary pressure. The β-blocking drugs propranolol, metoprolol and sotalol restored the ability of the ischemic vasculature to autoregulate, reduced the pressure gradient across the stenotic segment and decreased the resistance to flow at that site. Depending on the relative changes in stenosis resistance and distal bed resistance, total coronary blood flow to the ischemic area may increase, decrease or not change after β blockade. In the present study, total coronary blood flow did not consistently increase through the stenotic segment after β-receptor blockade (23 ± 2 to 29 ± 2 ml/min) (table 1). This may have been the result of a decrease in oxygen demand of the ischemic area, therefore allowing this area to regulate its blood flow. If oxygen demand decreased sufficiently, total coronary blood flow might also decrease through the stenosis by means of autoregulation.

**Clinical Implications**

Because of species differences, anesthesia and surgery, the results of the present study cannot be directly extrapolated to man. Beta-adrenergic-receptor blocking agents may reduce myocardial ischemia primarily by decreasing myocardial oxygen demand; by restoring autoregulation and increasing resistance of the subepicardium, these agents may shift flow to the subendocardium of ischemic areas. Although a poor correlation (r = 0.24) was found between the decrease in stenosis resistance and increase in subendocardial blood flow, these results suggest that another mechanism by which β blockade may exert important beneficial actions in myocardial ischemia is a decrease in the dynamic severity of a noncircumferential coronary artery stenosis. This may be part of the reason why β-receptor antagonists are more effective in patients with some antegrade flow in stenosed coronary arteries.

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Comparison of Degree and Extent of Coronary Narrowing by Atherosclerotic Plaque in Anterior and Posterior Transmural Acute Myocardial Infarction

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SUMMARY The percentage of cross-sectional area narrowing by atherosclerotic plaques in each 5-mm-long segment of the right, left main, left anterior descending and left circumflex coronary arteries was determined at necropsy in 50 patients who died of a first acute transmural myocardial infarction (AMI). The amount and extent of the coronary narrowing were compared in the 22 patients with anterior wall AMI and in the 28 patients with posterior wall AMI. Although the percentage of coronary arteries narrowed 76–100% was similar in the anterior and posterior wall AMI patients (74% vs 75%; average 3.0 of 4 coronary arteries per patient), the patients with anterior wall AMI had less severe narrowing of each of the 5-mm segments of the four major coronary arteries than did the patients with posterior wall AMI. Of the 1166 5-mm coronary segments examined in the 22 anterior wall AMI patients, 23% were narrowed 76–100% in cross-sectional area by atherosclerotic plaque, and of the 28 patients with posterior wall AMI, 39% of the segments were 76–100% narrowed (p < 0.001). Among the anterior AMI patients, a higher percentage of the 5-mm segments of the left anterior descending coronary artery was severely (> 75%) narrowed than either posterior perfusing coronary artery. The percentage of segments narrowed 76–100% for each of the major coronary arteries in the posterior AMI patients, however, was similar. Thus, our necropsy patients with posterior wall AMI had more extensive and severe coronary artery narrowing than did our patients with anterior wall AMI. If the coronary arteries had not been examined quantitatively, this difference in severity would not have been apparent.

PATIENTS with acute myocardial infarction (AMI), with rare exception, have severe narrowing by atherosclerotic plaques of at least one and usually two or more of the four major epicardial coronary arteries. Little information is available on the amount of coronary narrowing in patients who have anterior compared with those who have posterior ("inferior") wall left ventricular infarcts. Little information is also available on the amount of narrowing by atherosclerotic plaques in the four major coronary arteries in patients with either anterior or posterior left ventricular infarcts. AMI of the anterior left ventricular wall is believed by many to indicate a severe "lesion" in the left anterior descending coronary artery and absent or lesser degrees of narrowing of the dominant posterior coronary artery. Similarly, a posterior AMI is generally considered to indicate a severe "lesion" in the right or left circumflex coronary arteries and absent or lesser degrees of narrowing of the left anterior descending coronary artery. We examined both qualitatively and quantitatively at necropsy each of the four major epicardial coronary arteries in 50 patients who died during their first transmural AMI.

Patients and Methods

At the Pathology Branch, National Heart, Lung, and Blood Institute, 209 patients with transmural AMI unassociated with valvular heart disease, congenital cardiovascular anomalies, coronary emboli, major systemic disease or aortocoronary bypass operation have been studied. One hundred forty-nine patients were excluded from this analysis because the four major epicardial coronary arteries were unavailable for detailed histologic examination or...
Changes in ischemic blood flow distribution and dynamic severity of a coronary stenosis induced by beta blockade in the canine heart.
J D Buck, H F Hardman, D C Warltier and G J Gross

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