Effect of Beta-Adrenergic Suppression by Propranolol on Coronary Collateral Development in Response to Chronic Coronary Ischemia in Dogs

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SUMMARY Acute left circumflex coronary artery (LC) occlusion in conscious dogs caused marked ischemia in the myocardium supplied by the occluded artery, as judged by the radioactive microsphere technique for determining blood flow distribution. With the chest open, LC pressure distal to the occlusion fell to 21 ± 1.9% of aortic pressure.

By 8 weeks after gradual LC occlusion with an ameroid constrictor, collateral development had restored coronary blood flow distribution to near-normal under basal conditions and during pacing, at a heart rate of 200 beats/min. The only evidence for ischemia was in the subepicardium within the distribution of the unoccluded left anterior descending artery, which provided the extra collateral blood flow. Distal LC pressure was 70 ± 1.7% of aortic pressure.

Propranolol 160 mg orally every 6 hours for 8 weeks had no detectable effect on coronary collateral development, as judged by blood flow distribution or distal LC pressure. The only significant difference for the propranolol dogs was a slight transmural shift away from the subendocardium in the left anterior descending region.

BETA-ADRENERGIC SUPPRESSION by propranolol administration is widely used in the long-term management of patients with angina pectoris due to ischemic coronary heart disease. In patients limited by exertional angina, exercise capacity rises and the frequency of angina falls.1 2 Propranolol is known to lessen the increases in heart rate and myocardial O2 consumption that occur during exercise.3 4 Thus, a level of physical activity which initially surpassed the capacity of the coronary circulation to deliver O2, resulting in myocardial hypoxia, apparently can be sustained without inducing myocardial hypoxia when metabolic requirements for O2 are reduced by propranolol. In this way propranolol protects the patient against transient episodes of myocardial hypoxia and angina that occur during daily activity. The rationale of using this form of therapy assumes that such protection is desirable.

Coronary collateral vessels are associated with ischemic coronary artery disease. Although indicating underlying arterial disease, the collaterals themselves are desirable. They compensate in part for the obstructive coronary disease, restore perfusion of the myocardium toward normal, promote coronary reserve and may diminish the likelihood of myocardial infarction in the event of subsequent total occlusion of a stenosed coronary artery. Local myocardial hypoxia is believed to be an important stimulus for collateral development. The possibility of further enhancing collateral development by purposefully provoked temporary periods of myocardial hypoxia is one aspect of the rationale for advocating exercise training in patients with exertional angina pectoris.

If an increase in the frequency of transient myocardial hypoxia enhances collateral development, then an intervention that alternatively reduces the frequency of myocardial hypoxia might retard collateral development. This could be an important negative effect of long-term propranolol administration, which is masked by its other beneficial effects.

In this investigation we tested the hypothesis that chronic β-adrenergic suppression by propranolol interferes with the development of coronary collaterals in response to gradual coronary artery occlusion. We also reexamined the reports that acutely administered propranolol causes a transmural shift in coronary blood flow distribution in dogs with normal coronary circulations.5 7

Methods

Preliminary Operative Procedures

A left thoracotomy was performed using halothane anesthesia and aseptic technique. We encircled the proximal portion of the left circumflex coronary artery (LC) with an ameroid constrictor (2.77 or 3.0 mm internal diameter) for chronic LC occlusion experiments or pneumatic cuff occluder for acute LC occlusion experiments and closed the chest.

Experimental Conditions

Acepromazine (Ayerst), 1 mg/kg intravenously, and morphine, 30 mg intramuscularly, were administered for sedation, and 2% lidocaine was infiltrated subcutaneously for local analgesia. We inserted catheters into neck vessels and positioned them
by fluoroscopy in the left ventricle, thoracic aorta, and coronary sinus. We retrieved the proximal end of the cuff occluder through a skin incision on the dog’s back. With the dog awake and breathing spontaneously, heart rate and aortic and left ventricular blood pressures sensed by P23 Gb Statham transducers were recorded on a Brush Mark 200 ink writer, and microsphere injections were made to determine coronary blood flow distribution.

The dogs were then anesthetized using pentobarbital (approximately 15 mg/kg), and a wide left thoracotomy was carried out to measure pressures simultaneously in the aorta and in the LC immediately distal to the pneumatic cuff or ameroid.

Protocols

The acute effect of propranolol was investigated in six dogs with normal coronary circulation which had not had previous surgery. Observations were made with the dogs sedated and awake before and 20 minutes after intravenous injection of propranolol, 1 mg/kg.

Acute LC occlusion was performed in seven dogs 7–9 days after securing a pneumatic cuff on the LC. Patency of the LC initially was verified angiographically, and LC occlusion by cuff inflation was substantiated by reproducing the same electrocardiographic changes which occurred during the initial surgery. Observations were made with the dogs sedated and awake during: 1) control conditions, 2) 2–3 minutes after temporary acute LC occlusion achieved by inflation of the pneumatic cuff, and 3) 2–3 minutes after a second acute LC occlusion carried out during atrial pacing at a heart rate of 200 beats/min. Pacing was begun 20 minutes after release of the first occlusion, 5 minutes before the second occlusion. The dog then was anesthetized. With the chest open, aortic pressure (AP) and distal LC pressure (LCP) were measured simultaneously 2–3 minutes after LC ligation. The latter procedure was unsuccessful in three dogs, and we carried out the simultaneous LCP and AP measurements in three other dogs which had not undergone the remainder of the protocol.

The effect of chronic propranolol administration on coronary collateral development was investigated in 18 dogs in which gradual LC occlusion was produced by an ameroid constrictor. Propranolol 160 mg orally every 6 hours was begun in 10 dogs (body weight 22.1 ± 0.48 kg, mean ± SEM) 3 days after ameroid placement, and was continued for 8 weeks. The remaining eight dogs served as controls. At autopsy, the myocardium appeared grossly normal in all 18 dogs. We excluded two other dogs: one propranolol dog which had a myocardial infarction and one control dog which died suddenly after 5 weeks. All dogs remained sedentary in their cages. Collateral function was assessed at the end of 8 weeks; propranolol therapy was discontinued 21 hours earlier. Observations were made initially with the dog sedated and awake under resting conditions and 10–15 minutes after increasing the heart rate to 200 beats/min by atrial pacing. Complete LC occlusion and the presence of epicardial collaterals from the left anterior descending artery (LAD) to the distal LC were verified angiographically. We then measured simultaneous LCP and AP with the dog anesthetized and the chest open.

Microsphere Techniques

The spheres (3M Co) were approximately 15 μ in diameter and labelled with either strontium-85, cerium-141 or niobium-95, used in random sequence. Four hundred thousand to 1 million microspheres were introduced via the left ventricular catheter over a 15–20-second period. At the completion of the experiment, we removed the heart and separated the free wall of the left ventricle into regions supplied by the LAD and LC, based on the distribution of visible epicardial branches. Approximately 5 g of myocardium in which the distal branches of the LAD and LC met near the apex were discarded. We cut the LAD and LC regions into blocks and sliced each into inner (subendocardial) and outer (subepicardial) halves. All samples were placed in 15 mm diameter glass tubes and weighed, and their radioactive emissions were counted in a Packard 5230 automatic gamma spectrometer system, calibrated with cesium-137 as a standard before each run. Coronary blood flow data are expressed only as distribution ratios between different regions of the heart. These ratios depend simply upon the counts/min per gram (attributable to the isotope administered) for one region divided by that of the other.

Statistics

Statistical significance of differences was judged by a two-tailed t test, paired or unpaired as indicated.

Results

Acute Effect of Propranolol

Initial control heart rate (74 ± 6.3 beats/min, mean ± SEM), aortic blood pressure (111 ± 4.0/78 ± 3.6 mm Hg) and left ventricular end-diastolic pressure (7 ± 1.3 mm Hg) of these conscious sedated dogs with normal coronary arteries were comparable to values previously found in dogs trained to lie quietly without medication. Under these baseline conditions, propranolol 1 mg/kg intravenously caused no significant change in the hemodynamic parameters measured. There was no significant change in the distribution of coronary blood flow, as determined by microsphere concentration ratios, between different regions of the heart, or between the inner (subendocardial) and outer (subepicardial) layers of the left ventricular free wall (I/O) (table 1).

Beta-Adrenergic Suppression

During Chronic Propranolol Administration

Effectiveness of β-adrenergic blockade by the propranolol regimen was evaluated by the degree of
TABLE 1. Effects of Intravenous Propranolol 1 mg/kg on Coronary Blood Flow Distribution in Conscious Dogs (Means ± SEM for Six Dogs)

<table>
<thead>
<tr>
<th>Region</th>
<th>Percent of total heart spheres</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Right atrium</td>
<td>1.6 ± 0.17</td>
</tr>
<tr>
<td>Left atrium</td>
<td>1.9 ± 0.36</td>
</tr>
<tr>
<td>RV free wall</td>
<td>16.1 ± 0.79</td>
</tr>
<tr>
<td>Septum</td>
<td>34.9 ± 0.51</td>
</tr>
<tr>
<td>LV free wall</td>
<td>45.4 ± 1.34</td>
</tr>
<tr>
<td>Total heart</td>
<td>99.9</td>
</tr>
<tr>
<td>Inner/outer ratio</td>
<td></td>
</tr>
<tr>
<td>LV free wall</td>
<td>1.31 ± 0.928</td>
</tr>
</tbody>
</table>

Abbreviations: RV = right ventricular; LV = left ventricular.

...attenuation of the dogs' heart rate responses to intravenous isoproterenol injection (table 2). When the dogs were not receiving propranolol (control), 10 or 20 μg of isoproterenol caused a marked increase in heart rate. The heart rate increase from isoproterenol was mostly abolished (p < 0.001) when tested 2 hours or 5 hours after a 160 mg propranolol dose, midway through the 8-week period of chronic administration. Responsiveness to isoproterenol had returned nearly to the original control when tested at the end of 8 weeks, 21 hours after the last propranolol dose. Thus, study of the coronary circulation was carried out at a time when residual adrenergic blockade was minimal.

Coronary Collateral Function

Acute LC Occlusion

Experiments were done in conscious dogs with pneumatic cuff occluders encircling their LC. When the LC was patent before inflation of the pneumatic cuff, heart rate and aortic blood pressure were in the normal range (table 3, column 1), and coronary blood flow was evenly distributed between the LAD and LC regions of the left ventricular free wall (LC/LAD = 1.00 ± 0.027, table 4, column 1). Blood flow to the inner layer was greater than that to the outer layer (I/O > 1) in both regions, as in the dogs presented in table 1, which had had no previous heart surgery.

Acute LC occlusion for 2–3 minutes caused an increase in heart rate (p < 0.05) and a decrease in systolic aortic blood pressure (p < 0.01) (table 3). The myocardium supplied by the LC was markedly ischemic, especially the subendocardial region: LC/LAD blood flow was 0.24 ± 0.154 and I/O (LC) was 0.78 ± 0.12. I/O (LAD) was unaffected (table 4). Tachycardia (heart rate 200 beats/min) induced by pacing during a repeat acute LC occlusion caused a slight (p < 0.05) decrease in I/O (LAD), as found in dogs with intact coronary arteries. The further decreases in LC/LAD and I/O (LC) during tachycardia were not statistically significant.

Distal LC perfusion pressure and aortic pressure were measured 2–3 minutes after a third acute LC occlusion, with dogs anesthetized and their chests open. LCP/AP was 0.21 ± 0.019 (table 5).

Gradual LC Occlusion — Control

The center columns of tables 3–5 present data for the gradual LC occlusion-control dogs 8 weeks after implantation of the ameroid constrictor. Heart rate and aortic blood pressure were normal (table 3). Coronary blood flow distribution (table 4) under basal resting conditions was normal: LC/LAD and I/O values were almost identical to those of dogs with patent LC. Signs of LC ischemia did not even appear during induced tachycardia: LC/LAD remained essentially constant and I/O (LC) fell slightly, as in normal dogs. The only observed abnormality in the microsphere data occurred in the LAD region: I/O (LAD) did not decrease normally during tachycardia. LCP/AP (0.70 ± 0.17) was higher (p < 0.001) than in acute LC occlusion dogs (table 5).

Gradual LC Occlusion — Propranolol

The last columns of tables 3–5 present data for the dogs which received propranolol 160 mg orally every 6 hours for 8 weeks after implantation of the ameroid constrictor. These observations were made 21 hours after the last propranolol dose, when β-adrenergic inhibition had mostly dissipated. Heart rate and aortic blood pressure were not significantly different between control and propranolol dogs with gradual LC occlusion.

TABLE 2. Beta-Adrenergic Suppression by Propranolol Administration, 160 mg Orally (Mean ± SEM for 10 Dogs)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Time after dose (hrs)</th>
<th>Heart rate After intravenous isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rest 10 μg</td>
</tr>
<tr>
<td>Control</td>
<td>81 ± 5.6</td>
<td>158 ± 8.2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>75 ± 4.1</td>
<td>90 ± 4.2†</td>
</tr>
<tr>
<td></td>
<td>76 ± 4.0</td>
<td>92 ± 6.9†</td>
</tr>
<tr>
<td></td>
<td>81 ± 3.5</td>
<td>150 ± 7.2</td>
</tr>
</tbody>
</table>

Statistical significance—different from control:

* p < 0.05.
† p < 0.001.
Discussion

Administration of propranolol in anesthetized dogs has been reported to increase the left ventricular I/O and hence to improve subendocardial perfusion. We found that intravenous injection of propranolol in conscious sedated dogs had no demonstrable effect either on heart rate or coronary blood flow distribution, even though the dose we used was at least as large. It seems likely that propranolol affects the I/O in dogs with normal coronary arteries only indirectly when it simultaneously decreases an abnormally high initial heart rate, as has been suggested by others who found the change in I/O was abolished when heart rate was controlled. These data are consonant with the finding that when heart rate is constant, propranolol does not significantly change systolic or diastolic coronary blood flow.

The experiments with acute LC occlusion quantify the ability of preformed collateral connections to perfuse the myocardial region normally supplied by the LC. The LC perfusion pressure distal to the occlusion was only about 21% of AP, similar to previous reports. The microsphere data indicated that LC regional ischemia was severe (mean LC/LAD = 0.24), particularly in the inner layer (mean I/O (LC) = 0.78). The LAD region, in contrast, appeared to be unaffected. Although we cannot calculate numerical values for blood flow from our data, I/O (LAD) under basal resting conditions, and

Table 3. Heart Rate and Aortic Blood Pressure (Dogs Conscious) (Mean ± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patent LC (N = 7)</th>
<th>Acute LC occlusion 2–3 min (N = 7)</th>
<th>Gradual LC occlusion control 8 wks (N = 8)</th>
<th>Gradual LC occlusion propranolol 8 wks (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>65 ± 4.9</td>
<td>84 ± 6.9*</td>
<td>67 ± 5.6</td>
<td>73 ± 5.3</td>
</tr>
<tr>
<td>AP$_s$(mm Hg)</td>
<td>114 ± 3.3</td>
<td>104 ± 2.8†</td>
<td>117 ± 3.5</td>
<td>115 ± 3.0</td>
</tr>
<tr>
<td>AP$_d$(mm Hg)</td>
<td>77 ± 4.0</td>
<td>78 ± 4.4</td>
<td>75 ± 3.8</td>
<td>69 ± 4.0</td>
</tr>
</tbody>
</table>

Abbreviations: LC = left circumflex artery; N = number of dogs; HR = heart rate; AP = aortic pressure.

§$p < 0.05.
†$p < 0.01.

Table 4. Coronary Blood Flow Distribution as Determined by Relative Microsphere Concentrations (Dogs Conscious) (Mean ± SEM)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patent LC (N = 7)</th>
<th>Acute LC occlusion 2–3 min (N = 7)</th>
<th>Gradual LC occlusion control 8 wks (N = 8)</th>
<th>Gradual LC occlusion propranolol 8 wks (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LC/LAD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.00 ± 0.027†</td>
<td>0.24 ± 0.154</td>
<td>1.01 ± 0.017‡</td>
<td>1.07 ± 0.042‡</td>
</tr>
<tr>
<td>Pacing, HR = 200 beats/min</td>
<td>—</td>
<td>0.19 ± 0.063</td>
<td>1.02 ± 0.019‡</td>
<td>1.06 ± 0.031‡</td>
</tr>
<tr>
<td>I/O (LC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.28 ± 0.018†</td>
<td>0.78 ± 0.12</td>
<td>1.30 ± 0.070†</td>
<td>1.21 ± 0.034†</td>
</tr>
<tr>
<td>Pacing, HR = 200 beats/min</td>
<td>—</td>
<td>0.64 ± 0.17</td>
<td>1.13 ± 0.077*</td>
<td>1.02 ± 0.027*</td>
</tr>
<tr>
<td>I/O (LAD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>1.32 ± 0.037</td>
<td>1.24 ± 0.047</td>
<td>1.33 ± 0.049</td>
<td>1.18 ± 0.015§</td>
</tr>
<tr>
<td>Pacing, HR = 200 beats/min</td>
<td>—</td>
<td>1.03 ± 0.037</td>
<td>1.24 ± 0.040†</td>
<td>1.14 ± 0.018§</td>
</tr>
</tbody>
</table>

Abbreviations: LC = left circumflex artery; LAD = left anterior descending artery; N = number of dogs; HR = heart rate; I/O = inner/outer.

Statistical significance—Different from acute LC occlusion:
*$p < 0.05.$
†$p < 0.01.$
‡$p < 0.001.$

Different from gradual LC occlusion-control:
§$p < 0.05.$
even during induced tachycardia, was almost identical to values in these dogs before cuff inflation, as well as to values in other dogs with intact coronary arteries. The normal I/O (LAD) together with LC/LAD and I/O (LC) values similar to those found by others who selectively sampled the central ischemic region rather than the estimated entire LC region, as we did, suggests that our separation of LAD and LC regions was reasonably accurate and, moreover, is in keeping with data showing a steep gradient of ischemia separating normal and ischemic regions which, themselves, were relatively homogenous.

Previous studies indicate that propranolol exerts little, if any, effect on the regional ischemia in a similar acute LC occlusion model. A slight increase in I/O in both the ischemic and the normal regions was reported by Becker et al., but not by Kloner et al. Neither group found that propranolol brought about a significant change in the relative total transmural blood flows to the LC and LAD regions.

Our acute LC occlusion data provide a baseline from which interim collateral development can be measured in the gradual LC occlusion experiments. Collateral growth appears to begin within a few days of coronary ischemia and to level off 1–2 months after ameroind constrictor implantation. We carried out serial coronary angiography in two preliminary dogs and found that the LC occluded between 2 and 3 weeks of ameroind implantation, which is similar to findings of Scheel et al. Thus, in our chronic experiments the period available for collateral growth probably was 5–6 weeks.

The interim collateral development in the gradual LC occlusion dogs resulted in higher LCP/AP and normal LC/LAD and I/O (LC) under basal conditions, as found by others. Moreover, the constant LC/LAD during induced tachycardia implies that the collaterals in these dogs could maintain normal blood flow to the myocardial region originally supplied by the occluded artery, even under the physiologic stress of substantial increase in coronary circulatory needs. The slight decrease in I/O (LC) during tachycardia was nearly the same as in dogs with normal coronary arteries. This correlates with previous results showing that cardiac contraction impedes the blood flow within the myocardium which was delivered via collaterals, but exerts no additional compression of the epicardial collateral vessels themselves. The coronary collaterals that dogs develop in response to gradual coronary occlusion are remarkably effective in serving the myocardium originally supplied by the occluded artery. These new intercoronary connections, however, seem to exert a detectable impact on blood flow to the rest of the heart. The pattern of blood flow distribution in dogs with chronic LC occlusion compensated by collaterals was indistinguishable under basal resting conditions from that of dogs with intact coronary arteries (table 4). But, when tachycardia was induced, I/O decreased only in the region supplied by the new collaterals and in the LAD region supplied by the artery donating the additional collateral blood flow. Flameng et al. found that in dogs with chronic LC occlusion, blood flow in the subepicardium of the LAD region, although normal under basal conditions, did not increase normally during maximum vasodilation. The results imply that diversion of blood flow by collaterals may drain blood away from the outer myocardial layer of the region which supplies the extra collateral flow. We have no information to indicate whether this phenomenon is physiologically important.

If collateral growth is regulated to maintain a proper balance between coronary blood flow and myocardial metabolism requirements, one might suspect that chronic reduction in metabolic requirements by propranolol might retard collateral development. Although myocardial metabolic rate was not measured in these experiments, the marked attenuation of the heart rate response to isoproterenol injection during the interval between propranolol doses implies that transient increases in heart rate or inotropy from fluctuations in sympathetically activity would also be significantly reduced throughout the several weeks available for collateral development in these dogs.

There were, however, no significant differences in the LC/LAD and I/O (LC) values between propranolol and control gradual LC occlusion dogs, either under basal resting conditions or during induced tachycardia (table 4), and distal LC pressure was not significantly different for propranolol dogs (table 5). Thus, we found no evidence that chronic β-adrenergic suppression interfered with collateral development in response to LC occlusion, or with the compensatory decrease in resistance in the distal LC microcirculation needed to maintain normal blood flow with low perfusion pressure.

The impact of collaterals to the distal LC on

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**Table 5. Distal LC Perfusion Pressure (Open Chest Dogs) (Mean = SEM)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Acute LC occlusion 2–3 min (N = 7)</th>
<th>Gradual LC occlusion control 8 wks (N = 8)</th>
<th>Gradual LC occlusion propranolol 8 wks (N = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP (mm Hg)</td>
<td>89 ± 8.5</td>
<td>81 ± 10.5</td>
<td>80 ± 4.1</td>
</tr>
<tr>
<td>LCP (mm Hg)</td>
<td>19 ± 6.6</td>
<td>57 ± 7.5*</td>
<td>67 ± 5.5*</td>
</tr>
<tr>
<td>LCP/AP</td>
<td>0.21 ± 0.019</td>
<td>0.70 ± 0.017*</td>
<td>0.75 ± 0.039*</td>
</tr>
</tbody>
</table>

Abbreviations: LC = left circumflex artery; N = number of dogs; AP = mean aortic pressure; LCP = mean distal circumflex artery pressure.

Statistical significance—different from acute LC occlusion:

* p < 0.001.
transmural coronary blood flow within the LAD region also seemed to be unaffected by chronic β-adrenergic blockade. The decrease in I/O (LAD) which occurred in acute LC occlusion, which is normal, did not occur in hearts with chronic LC occlusion, with or without propranolol administration.

The lower I/O in the propranolol dogs implies relatively lower blood flow in the inner layer of the myocardium, which might be interpreted as a sign of poor perfusion. However, the lower I/O was not intensified by tachycardia and appeared to occur diffusely in the left ventricle (table 4), although reaching statistical significance in the LAD region only. The explanation for the low I/O is not clear, but it does not suggest to us impaired collateral development.

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**References**

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