Effects of Beta-Receptor Blockade on the Systemic and Coronary Hemodynamic Response to an Increasing Ventricular Rate in the Unanesthetized Dog

By Fred R. Cobb, M.D., Robert J. Boche, M.D., Paul A. Ebner, M.D., Judith C. Rembert, B.S., and Joseph C. Greenfield, Jr., M.D.

ABSTRACT

Phasic coronary and aortic blood flow and arterial pressure were measured as heart rates were increased by ventricular pacing from 120 to 270 beats/min in unanesthetized dogs before and after beta-receptor blockade with intravenous propranolol. Before beta-receptor blockade, coronary flow progressively increased and coronary vascular resistance decreased with increasing heart rates. Aortic blood flow and arterial pressure were not significantly altered at rates below 240 beats/min. After administration of propranolol, mean coronary blood flow was comparable to that before beta-receptor blockade at heart rates from 120 to 210 beats/min. However, aortic flow progressively decreased and peripheral resistance increased with increasing ventricular rates. At heart rates above 210 beats/min after propranolol coronary vascular resistance increased and coronary flow decreased. These data ascribe considerable importance to beta-receptor activity in the normal hemodynamic adjustments to rapid heart rates.

ADDITIONAL KEY WORDS
propranolol pacemaker
blood flow electromagnetic flowmeter

Beta-receptor activity has been demonstrated in the myocardium (1), the systemic arterial (1) and venous vascular systems (2), and the coronary arteries (3-6). The role and relative importance of these receptors in the regulation of cardiac function has not been evaluated completely. Some observers have ascribed major importance to the sympathetic nervous system (7, 8), whereas others have found that the overall performance of the heart was minimally affected by the adrenergic nerves (9).

The effect of heart rate on coronary and systemic hemodynamics has been the subject of study for many years. More recent studies have indicated that coronary blood flow is augmented by increasing heart rates (10-13), and that there exists a narrow range of heart rates at which maximum cardiac output and arterial blood pressure occur (13-14).

The purpose of this study was to examine the systemic and coronary hemodynamic responses to an increasing ventricular rate in unanesthetized dogs. Using propranolol to block beta receptors, an attempt was made to evaluate the importance of beta-receptor activity in the normal cardiovascular adjustment to an increasing ventricular rate.

Method

Six mongrel dogs weighing 20 to 25 kg were anesthetized with pentobarbital, 30 mg/kg, and...
ventilated with a Harvard respirator. Through a left thoracotomy, the proximal 1.5 cm of the left circumflex coronary artery and the root of the aorta were dissected free. A Statham electromagnetic flowmeter Q probe was placed around the aorta and an ST probe around the left circumflex coronary artery. Care was taken to prevent constriction or torsion of either vessel. Circumferential silastic strips proximal and distal to the aortic probe cushioned it to retard erosion into the aorta. A polyethylene snare placed around the left circumflex coronary artery distal to the flow probe and proximal to any branch allowed temporary complete occlusion of blood flow to ascertain a zero flow baseline. The sinus and A-V nodes were electrocardiogram was obtained. Aortic and coronary blood flows were measured with Statham P23Db transducers. The coronary snare was exteriorized dorsally through a small separate incision at the base of the neck. The coronary snare was tunneled subcutaneously so that it could be exteriorized by a 1-cm incision at the time of the study.

Studies were performed 7 to 10 days after surgery with the animals loosely restrained and lying quietly on their right sides. Initial sedation was obtained by intravenous administration of 10 to 20 mg of morphine sulfate. After subcutaneous infiltration with lidocaine hydrochloride, the femoral artery was exposed and a no. 7 French Lehman cardiac catheter inserted and advanced into the descending aorta for pressure monitoring, with a Statham P23Db transducer. The coronary snare was exteriorized. Lead II of a standard electrocardiogram was obtained. Aortic and coronary blood flows were measured with Statham Model M-4000 electromagnetic flowmeters. Flowmeter outputs were divided so that phasic and electrically integrated mean flows could be recorded simultaneously. Flowmeter calibration was performed by passing measured flows of normal saline through an artery and its surrounding probes. Prior studies have demonstrated that use of saline instead of blood increases the sensitivity of the electromagnetic flowmeter approximately 5%. However, varying the hematocrit of blood from 20 to 45% did not influence the calibration (15). Calibration factors for aortic probes remained within a standard deviation of ± 4% during the period of study. Calibration factors for coronary probes were within a standard deviation of ± 7%. Data were recorded on a Sanborn Model 850 eight-channel direct-writing oscillograph and a Hewlett-Packard 3917-A magnetic tape recorder.

After catheterization, data were continuously recorded for 30 to 45 minutes while the animal adjusted to the laboratory environment. During this interval, coronary blood flow and other hemodynamic variables attained resting levels that were maintained throughout the remainder of the study. Pacing was then begun, using a Grass Model 54 Physiologic Stimulator that delivered a square-wave pulse of 3-msec duration 10% above threshold voltage through an isolation unit. As permitted by the sinus rate, atrial pacing was begun at either 90 or 120 beats/min and continued for 3 minutes. Observing a 5-minute interval between pacing periods, atrial pacing was repeated in increments of 30 beats/min until second-degree atrioventricular block occurred. Ventricular pacing was then begun at the lowest rate that prevented atrial interference; this was always between 90 and 120 beats/min. The pacing rate was maintained for 3 minutes and samples of data obtained during the second and third minutes of pacing were compared to ensure that a steady state had been achieved. An interval of 5 minutes from the time all hemodynamic variables returned to the control level was allowed between pacing periods. Frequent brief periods of coronary occlusions were used to ensure correct zero baseline for the coronary flow. To measure residual coronary vasodilator capacity at ventricular rates of 240 beats/min and above, 5- to 10-second occlusions were produced during repeat pacing periods.

Reactive hyperemia was observed during sinus rhythm following two 10-second periods of coronary occlusion 15 minutes apart. Excess blood flow occurring during the hyperemic period was determined by electrical integration using a Donner Model 3400 analog computer. The blood flow debt incurred during the occlusion period was defined as the mean flow prior to occlusion (cm³/sec) multiplied by duration of occlusion (sec). Percent blood flow debt repayment was determined by dividing the excess blood flow during the reactive hyperemia by the blood flow debt and multiplying the result by 100.

After the initial sequence of pacing, propranolol, 0.2 mg/kg, was injected intravenously to effect beta-receptor blockade and the ventricular pacing sequence was repeated. Effectiveness of blockade was ensured before pacing and again at the end of each study by intravenous infusion of isoproterenol. If the study exceeded 45 minutes or when complete blockade to infusion of isoproterenol, 3 µg/min, was not achieved initially, the dosage of propranolol was repeated. Since hemodynamic deterioration occurred at approximately 30 beats/min less than the maximum rate accomplished before beta-receptor blockade, com-
Results observed in a typical experiment during ventricular pacing are illustrated in Figure 1. The pattern of phasic coronary blood flow is similar to that previously reported in the resting unanesthetized dog: a diastolic plateau, which at slow heart rates fell gradually with the arterial pressure, and a smaller systolic flow marked by a variable positive spike during early ventricular ejection. Flow minima were observed immediately before the onset of left ventricular ejection and as ejection terminated; the latter flow minimum approached or attained zero at slow heart rates, but both minima progressively increased in magnitude as heart rates were increased. In the study illustrated in Figure 1, mean coronary flow increased from 49.5 to 77.0 cm³/min as the heart rate was increased from 126 to 254 beats/min. There was little change in arterial pressure and mean aortic flow. Changes in beat-to-beat aortic flow often occurred at rapid rates (Fig. 1, C), and 10- to 20-second periods of pulsus alternans were occasionally observed at rates above 200 beats/min. There was no significant alteration of mean aortic blood flow, mean arterial pressure, or mean coronary blood flow during pulsus alternans.

Table 1 and Figures 2 and 3 include mean
TABLE 1
Effects of Beta-Receptor Blockade Produced by Propranolol on Coronary Blood Flow and Mean Coronary Vascular Resistance at Three Heart Rates

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Coronary blood flow (cm³)</th>
<th>Coronary blood flow min (cm³/min)</th>
<th>Coronary vascular resistance (dyne-sec-cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>123</td>
<td>0.300 ± 0.045</td>
<td>0.050 ± 0.010</td>
<td>0.250 ± 0.035</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>0.270 ± 0.025</td>
<td>0.050 ± 0.005</td>
</tr>
<tr>
<td>178</td>
<td>0.270 ± 0.035</td>
<td>0.060 ± 0.010</td>
<td>0.210 ± 0.025</td>
</tr>
<tr>
<td>176</td>
<td>+</td>
<td>0.250 ± 0.025</td>
<td>0.060 ± 0.010</td>
</tr>
<tr>
<td>200</td>
<td>0.205 ± 0.045</td>
<td>0.050 ± 0.010</td>
<td>0.155 ± 0.025</td>
</tr>
<tr>
<td>200</td>
<td>+</td>
<td>0.135 ± 0.015</td>
<td>0.035 ± 0.010</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ±1 SEM.

coronary hemodynamic measurements from the six animals as ventricular rates were increased from 120 to 270 beats/min. Control measurements for each animal were made at 120 beats/min, since in all cases ventricular pacing at this rate was possible without atrial interference. Before administration of propranolol, mean coronary blood flow increased directly with ventricular rate to reach a maximum of 51% above the control value at 240 beats/min (P<0.001) (Fig. 2). No further increase in coronary flow occurred at rates above 240 beats/min. Mean coronary vascular resistance decreased with increasing heart rate throughout the entire range of pacing rates; the minimum mean coronary resistance attained was 57% of that at a ventricular rate of 120 beats/min (P<0.001) (Fig. 2). Diastolic coronary flow per beat decreased progressively with increasing heart rate and accounted for the decrease seen in total coronary flow per beat (Fig. 3). In contrast, systolic coronary flow per beat remained relatively constant over the entire range of heart rates. Consequently, systolic coronary flow per minute increased directly with heart rate (Figs. 2 and 3).

During pacing at 240 beats/min, a further increase in coronary flow could be elicited by producing a brief coronary occlusion, indicating that vasodilator capacity was still present. Periods of hyperemic flow during which coronary flow exceeded that attained during the pacing period frequently followed pacing at the highest ventricular rates. Immediately following pacing at 260 beats/min, mean coronary blood flow increased from 54.0 cm³/min to 65.3 cm³/min (P<0.05) and then gradually fell, attaining the control level 150 sec after discontinuing ventricular pacing.

Cardiac output and mean arterial pressure were not significantly altered at rates of 120 to 240 beats/min. Both decreased slightly at rates above 240 beats/min (P<0.02) (Fig. 4). The tension-time index increased progressively to 30% above the control value as ventricular rates were increased from 120 to 180 beats/min (P<0.01) (Fig. 4, Table 2). No further increase in the tension-time index occurred at heart rates above 180 beats/min. This plateau

Circulation Research, Vol. XXV, September 1969
Effects of beta-receptor blockade

Effects of increasing heart rate produced by ventricular pacing on normalized coronary blood flow (CBF) per minute, mean coronary vascular resistance (CVR), and systolic coronary blood flow. Systolic coronary flow is expressed as a percentage of the total coronary blood flow. Values are mean ± 1 SEM.

Of the tension-time index occurred despite no significant reduction of systolic ejection pressure until ventricular rates exceeded 240 beats/min. Regression of normalized coronary blood flow on normalized tension-time index for all animals simultaneously resulted in a correlation coefficient 0.40. Considering only heart rates below 200 beats/min improved this correlation coefficient to 0.52.

Second-degree atrioventricular block generally prevented atrial pacing above 120 beats/min. In two animals, however, atrial pacing without heart block was possible to 150 beats/min. Within this range, hemodynamic measurements were not significantly different for atrial or ventricular pacing.

The coronary hemodynamic effects of propranolol administered during sinus rhythm are shown in Table 3. Propranolol produced no significant change in heart rate, resting coronary blood flow, or the reactive hyperemic response to a brief coronary occlusion. Likewise, at a paced ventricular rate of 120 beats/min, propranolol produced no significant change in mean coronary blood flow or mean coronary resistance (Table 1). At this rate administration of propranolol decreased mean cardiac output 11% and increased peripheral vascular resistance 22%, neither change being statistically significant.

As ventricular rates were increased from 120
Effects of Beta-Receptor Blockade Produced by Propranolol on Arterial Blood Pressure, Aortic Blood Flow, Peripheral Vascular Resistance, Duration of Ejection and Tension-Time Index at Three Heart Rates

<table>
<thead>
<tr>
<th>Heart rate (beats/min)</th>
<th>Propranolol</th>
<th>Blood pressure (mm Hg)</th>
<th>Aortic flow (cm³/min)</th>
<th>Peripheral resistance (dyne-cm sec⁻¹)</th>
<th>Duration of ejection (sec)</th>
<th>Tension-time index (mm Hg sec/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>123</td>
<td>0</td>
<td>±10/8</td>
<td>2020</td>
<td>±410</td>
<td>0.160</td>
<td>2550</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>±12/8</td>
<td>1720</td>
<td>±580</td>
<td>0.165</td>
<td>2610</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
</tr>
<tr>
<td>178</td>
<td>0</td>
<td>±8/8</td>
<td>1950</td>
<td>±370</td>
<td>0.133</td>
<td>820</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>±10/8</td>
<td>1600</td>
<td>±700</td>
<td>±0.004</td>
<td>±0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
</tr>
<tr>
<td>260</td>
<td>0</td>
<td>±10/8</td>
<td>1590</td>
<td>±370</td>
<td>±0.03</td>
<td>±0.03</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>±14/10</td>
<td>820</td>
<td>±820</td>
<td>±0.002</td>
<td>±0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>N.S</td>
<td>N.S</td>
<td>N.S</td>
</tr>
</tbody>
</table>

Values are mean ±SEM.

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To 210 beats/min the incremental changes in total coronary flow, coronary resistance, and diastolic coronary flow with increasing heart rate were essentially unchanged by administration of propranolol (Fig. 2). Unlike the control situation, however, at ventricular rates above 210 beats/min, dogs that had received propranolol showed a marked decrease in coronary flow (P < 0.01) with an increase in mean coronary resistance (P < 0.03) (Fig. 2). This was accompanied by a 10% reduction of mean arterial pressure (P < 0.02). Upon termination of pacing at 260 beats/min, mean coronary blood flow immediately increased from 35.5 to 57.6 cm³/min and then gradually fell to the control level. Although this increase in the rate of coronary flow following pacing (mean change = +22.1 cm³/min, P < 0.05) was greater than that observed following the same pacing rate before administration of propranolol (mean change = +11.3 cm³/min, P < 0.05), the time required for this hyperemic flow to fall to the control level was not significantly different from the control (140 and 150 sec, respectively).

In contrast to the control, administration of propranolol resulted in a progressive decline in cardiac output with increasing heart rates; this was accompanied by a progressive increase in peripheral vascular resistance (Fig. 4). Propranolol produced no significant alteration of arterial blood pressure or the tension-time index at heart rates between 120 and 210 beats/min (Fig. 4). Pulsus alternans did not occur more frequently after administration of propranolol. Although all dogs could maintain a ventricular rate of 270 to 300 beats/min before the administration of propranolol without serious decline in cardiac output or arterial pressure, five or six could not sustain these rates after beta-receptor blockade because of precipitous declines in cardiac output with mean arterial pressures of less than 50 mm Hg.

**Discussion**

Before beta-receptor blockade, coronary blood flow increased as a direct function of heart rate between 90 and 240 beats/min. This increase occurred despite insignificant changes in mean arterial pressure or cardiac output. These data support previous studies in anes-
Effects of increasing heart rate produced by ventricular pacing on normalized aortic blood flow (AoF), mean arterial pressure (MAP), peripheral vascular resistance (PVR), and tension-time index (TTI). Values are mean ± 1 SEM.

Effects of beta-receptor blockade on coronary blood flow, mean arterial pressure, and peripheral vascular resistance are shown in Figure 4. Graphs display the data for both control and propranolol conditions. The graphs indicate that beta-receptor blockade generally decreases coronary blood flow and peripheral vascular resistance, with a significant reduction in coronary blood flow observed at rapid heart rates.

Miller and associates (14) and Pitt and Gregg (13), using anesthetized dogs with complete heart block, observed an "optimum" ventricular rate of approximately 150 beats/min, above or below which cardiac output and mean arterial pressure declined. The ability to maintain cardiac output and arterial pressure at considerably higher rates in the present study and that of Maxwell and associates (11) may be related to changes produced by chronic complete heart block in previous studies. Ventricular dilatation or hypertrophy may occur in dogs with chronic complete heart block, and may be accompanied by evidence of congestive heart failure (16). Although overt cardiac decompensation was observed in only one animal of the group studied by Miller and associates (14), it is possible that subtle alterations occurred which impaired the ability of the ventricle either to fill or to eject blood at rapid heart rates.

Pitt and Gregg (13) observed little change in coronary flow, mean arterial pressure or cardiac output after beta-receptor blockade when ventricular rates were controlled between 50 and 150 beats/min in unanesthetized dogs with complete heart block. Likewise, in the present study at slow heart rates beta-receptor blockade produced no significant change in coronary blood flow or mean coronary vascular resistance. Contrary to these findings, Parratt (5) and McKenna and associates (17), observed in studies on anesthetized dogs that following beta-receptor blockade coronary flow decreased 29 to 34% and peripheral vascular resistance increased 32 and 42% while heart rate decreased 18 and 11%, respectively. Since measurements were not reported at comparable rates before and after beta-receptor blockade, changes in coronary hemodynamics may have resulted in part from changes in heart rate. In addition, in these studies general anesthesia may have resulted in activation of the sympathetic nervous system not present in the normal state (18). Beta-receptor blockade might then be expected to result in the hemodynamic changes observed.

The repayment of reactive hyperemia blood flow debt observed following 10-second coronary occlusion was comparable to that reported by Olsson and Gregg (19) in anesthetized dogs (500 ± 200%). They found that the hyperemic response to temporary coronary occlusion was not significantly altered by prior treatment with atropine or guanethidine. The lack of effect of propranolol on reactive
TABLE 3
Effects of Beta-Receptor Blockade on Resting Coronary Blood Flow and Reactive Hyperemia after a Brief Coronary Occlusion during Sinus Rhythm

<table>
<thead>
<tr>
<th>Dog</th>
<th>Heart rate (beats/min)</th>
<th>Control coronary flow (cm²/min)</th>
<th>Duration of occlusion (sec)</th>
<th>Peak coronary flow (cm²/min)</th>
<th>Duration of reactive hyperemia (sec)</th>
<th>Reactive hyperemia debt repaid %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 C</td>
<td>72</td>
<td>36.6</td>
<td>9.8</td>
<td>101.5</td>
<td>86</td>
<td>571</td>
</tr>
<tr>
<td>1 P</td>
<td>72</td>
<td>36.6</td>
<td>10.5</td>
<td>108.3</td>
<td>100</td>
<td>532</td>
</tr>
<tr>
<td>2 C</td>
<td>95</td>
<td>27.4</td>
<td>11.0</td>
<td>95.9</td>
<td>104</td>
<td>636</td>
</tr>
<tr>
<td>2 P</td>
<td>90</td>
<td>24.8</td>
<td>10.0</td>
<td>98.5</td>
<td>88</td>
<td>488</td>
</tr>
<tr>
<td>3 C</td>
<td>74</td>
<td>28.8</td>
<td>11.5</td>
<td>116.6</td>
<td>104</td>
<td>855</td>
</tr>
<tr>
<td>3 P</td>
<td>68</td>
<td>21.1</td>
<td>9.5</td>
<td>86.8</td>
<td>101</td>
<td>834</td>
</tr>
<tr>
<td>4 C</td>
<td>72</td>
<td>27.4</td>
<td>15.5</td>
<td>89.3</td>
<td>84</td>
<td>634</td>
</tr>
<tr>
<td>4 P</td>
<td>76</td>
<td>27.0</td>
<td>15.2</td>
<td>103.4</td>
<td>77</td>
<td>670</td>
</tr>
<tr>
<td>5 C</td>
<td>92</td>
<td>21.7</td>
<td>9.3</td>
<td>83.4</td>
<td>72</td>
<td>669</td>
</tr>
<tr>
<td>5 P</td>
<td>94</td>
<td>18.0</td>
<td>9.5</td>
<td>67.8</td>
<td>55</td>
<td>649</td>
</tr>
<tr>
<td>6 C</td>
<td>126</td>
<td>41.1</td>
<td>10.6</td>
<td>103.6</td>
<td>86</td>
<td>623</td>
</tr>
<tr>
<td>6 P</td>
<td>114</td>
<td>41.5</td>
<td>10.2</td>
<td>94.2</td>
<td>127</td>
<td>679</td>
</tr>
</tbody>
</table>

Mean ± SEM

C 89 ± 9 30.5 ± 3.0 11.3 ± 0.9 98.4 ± 4.8 89 ± 5 665 ± 40
P 86 ± 8 28.2 ± 3.7 10.8 ± 0.9 93.2 ± 5.9 91 ± 10 642 ± 50

C = control before administration of propranolol. P = propranolol. Propranolol produced no significant change in mean values.

hyperemia in the present study further militates against neural mechanisms in the production or control of coronary reactive hyperemia.

The progressive decrease in cardiac output as ventricular rates were increased from 120 to 210 beats/minute following beta-receptor blockade suggested that sympathetic activity had been of importance in maintaining a stable cardiac output with increasing ventricular rates. The progressive increase in peripheral vascular resistance coincident with decreasing cardiac output after beta-receptor blockade suggested also sympathetic activation of unblocked alpha receptors. Between 120 and 210 beats/min, the rate-induced changes in total coronary blood flow, mean coronary resistance, and diastolic coronary flow were essentially similar to those before beta-receptor blockade despite the striking differences in cardiac output and peripheral vascular resistance. However, stroke systolic coronary flow, which did not change significantly within this range prior to beta-receptor blockade, increased 10 to 20% after administration of propranolol. In contrast, Pitt and Gregg (13), using unanesthetized dogs with chronic complete heart block, reported that propranolol produced no change in the response of stroke systolic coronary flow to heart rate. No explanation for the disparity between these findings is apparent. It is possible, however, that in those studies coronary blood flow responses were affected by cardiovascular alterations with chronic complete heart block (16).

Unlike the control, at heart rates above 210 beats/min beta-receptor blockade resulted in a significant increase in mean coronary resistance with a marked decline in coronary blood flow. At these rates, mean arterial pressure decreased to 10% below the control level and may have accounted for some of the reduction in coronary flow. A comparable decrease in mean arterial pressure recorded before beta-receptor blockade at the next higher rate (Fig. 4), however, did not result in reduction of coronary flow, suggesting that...
factors other than changes in perfusion pressure were operative after beta-receptor blockade. In studies on anesthetized dogs with heart rates between 110 and 200 beats/min, Mosher and associates (20) found little change in coronary flow when coronary perfusion pressure was reduced selectively from 120 to 70 mm Hg. It is possible, however, that at the high flow rates observed in the present study during rapid pacing, coronary blood flow may be more pressure dependent.

The factors responsible for the marked augmentation of coronary blood flow at rapid ventricular rates have not been evaluated completely. Several investigators have found a correlation related to heart rate between coronary blood flow and myocardial oxygen consumption (10-12). Several factors are known to contribute to increased myocardial oxygen requirements during rapid heart rates. Sarnoff and associates (21) emphasized that the tension-time index (systolic ejection time/minute × mean systolic ejection pressure) is closely correlated with myocardial oxygen requirements. In the present study there was an increase in ejection time per minute with little change in mean systolic pressure at heart rates up to 200 beats/min. Thus, within this range, the mean tension-time index progressively increased with coronary flow. Although statistically significant, this appeared to be an imprecise relationship, however, since linear regression analysis of coronary blood flow on the tension-time index within this range resulted in an overall correlation coefficient of only 0.52. In addition, at rates above 200 beats/min coronary flow continued to increase while the tension-time index leveled off or declined. These observations suggest that other factors were involved in the augmentation of coronary blood flow at rapid ventricular rates.

In the present study, significant coronary hemodynamic effects of beta-receptor blockade were confined to rates above 200 beats/min, suggesting that reflex sympathetic stimulation occurred in that range. Sonnenblick and associates (22) have emphasized that increased initial contraction velocity, as may be produced by sympathomimetic agents, is an important determinant of myocardial oxygen requirement and thus coronary flow. No measurement of initial contraction velocity was attempted in these studies.

Recent studies have suggested that sympathetic stimulation may also influence coronary flow by direct stimulation of intracoronary beta receptors. Beta-receptor activity has been demonstrated in isolated coronary artery strips (3), in the nonbeating heart (4), and in coronary arteries of anesthetized (5) and unanesthetized dogs (6). Pitt and associates (6) have shown that stimulation of intracoronary beta receptors may increase coronary flow as much as 100% independently of myocardial or systemic hemodynamic effects. If reflex sympathetic activation at rapid ventricular rates normally resulted in direct coronary vasodilation, beta-receptor blockade might be expected to eliminate that response, or to convert it to a constrictor response by enhancement of intracoronary alpha-receptor activity (5, 6, 23). However, simultaneous blockade of myocardial beta receptors with possible resultant changes in contractile force which also affect coronary flow prevents accurate assessment of the relative importance of intracoronary adrenergic receptors in the adjustment to rapid ventricular rates.

Whitsitt and Lucchesi (24) observed that the isomer d-propranolol, which has little beta-receptor blocking activity, increased coronary vascular resistance in 10 of 15 open-chest dogs tested. In these 10 dogs d-propranolol produced increases in coronary resistance comparable to that produced by dl-propranolol when rate was held constant or after preceding treatment with reserpine. They concluded that propranolol may reduce coronary blood flow by a nonspecific myocardial depressant effect that occurs independently of beta-receptor inhibition. Their animals appeared to have abnormally increased sympathetic stimulation, however, since resting heart rates were high (mean rate = 160 beats/min), and decreased 27% after propranolol. The
present findings and those of Pitt and Gregg (13) do not substantiate this finding in the unanesthetized dog, since no significant changes in resting coronary flow or resistance were produced by propranolol.

At rapid ventricular rates beta-receptor blockade may potentially reduce coronary blood flow by reducing myocardial oxygen requirements, by decreasing central aortic pressure, by blocking the vasodilator effect of intracoronary beta receptors, or by enhancing intra coronary alpha-receptor activity. The present study indicates that in the dog propranolol may severely compromise the hemodynamic adjustments to rapid ventricular rates and suggests that reflex beta-receptor stimulation in the coronary arteries or myocardium may be important in augmenting coronary flow and maintaining cardiac output.

Acknowledgment
The authors gratefully acknowledge the technical assistance of Mrs. Kathleen Smith, Miss Debbie Hilliard and Mr. Kirby Cooper. The department of Medical Illustration of the Durham Veterans Administration Hospital rendered valuable support.

References


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Circ Res. 1969;25:331-341
doi: 10.1161/01.RES.25.3.331

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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