The Myocardial Depressant Effect of Beta-Receptor Blocking Agents

COMPARATIVE STUDY OF \(\text{dL-PROPRANOLOL, d-PROPRANOLOL, AND PRACTOLOL IN AWAKE DOGS WITH AND WITHOUT ACUTE MYOCARDIAL INFARCTION}

By Chang-seng Liang and William B. Hood, Jr.

ABSTRACT

\(\text{dL-Propranolol, d-propranolol, and practolol were administered in increasing doses to conscious dogs before and after acute coronary artery occlusion. dL-Propranolol and practolol caused dose-dependent decreases in cardiac output, stroke volume, stroke work, and maximum rate of left ventricular pressure rise before and after coronary artery occlusion. These parameters were reduced 25\%-40\% after the largest cumulative doses—1.43 mg/kg for dL-propranolol and 52 mg/kg for practolol—were administered. The degree of beta-receptor blockade increased in proportion to the logarithm of plasma drug concentration. After occlusion, both drugs produced identical decreases in cardiac output at equivalent degrees of beta-receptor blockade. Neither drug affected resting heart rate before infarction, and neither drug reduced the tachycardia induced by coronary artery occlusion; this tachycardia response probably resulted from cardiac vagal withdrawal. Mean systemic arterial blood pressure and total peripheral vascular resistance increased following beta-receptor blockade before infarction, most likely because of increased peripheral vascular alpha-adrenergic activity. These two effects did not occur after coronary artery occlusion, probably because vascular alpha-adrenergic activity had already been stimulated. dL-Propranolol produced none of these effects. We concluded that the cardiodepressant effect of beta-receptor blocking agents in the doses administered was caused by their inhibition of endogenous sympathetic tone to the heart rather than by their quinidinelineike action.}

KEY WORDS coronary occlusion myocardial contractility isoproterenol-induced tachycardia cardiac output

Racemic propranolol is effective in the treatment of angina pectoris, cardiac arrhythmias, and certain other cardiovascular disorders (1\4). However, it can precipitate acute congestive heart failure in patients with impaired left ventricular function because of its myocardial depressant effect (1\5). dL-Propranolol possesses both beta-receptor-blocking and membrane-stabilizing (quinidinelineike) properties. Levy and Richards (6, 7) and Levy (8) have suggested that the effect of dL-propranolol on the myocardium is caused by its quinidinelineike action, because they found no correlation between the beta-receptor-blocking and myocardial depressant actions of several beta-receptor blocking agents on isolated left atrial preparations. Barrett (9), however, has ascribed the cardiodepressant effect of dL-propranolol to beta-receptor blockade, because dL-propranolol is less potent in depressing left ventricular function in anesthetized animals. Both dextro and levo isomers of propranolol are equipotent for quinidinelineike action, but d-propranolol is less than one-fiftieth as potent as dL-propranolol as a beta-receptor blocking agent (10, 11). The findings of Barrett (9) have subsequently been confirmed by other investigators (12, 13).

Practolol is a cardioselective beta-receptor blocking agent devoid of quinidinelineike action (14). It decreases cardiac output and maximum rate of left ventricular pressure rise and increases left...
ventricular end-diastolic pressure, indicating that left ventricular function can be reduced by inhibition of endogenous sympathetic tone to the heart alone (13, 15–18). However, it is difficult to compare practolol with dl-propranolol in these respects; in most studies, the degree of beta-receptor blockade has not been determined and experimental conditions are not strictly comparable from study to study.

In the present study, we compared the cardiovascular effects of dl-propranolol, d-propranolol, and practolol to evaluate their relative roles as beta-receptor blocking agents and quinidine-like agents in reducing myocardial contractility. Studies were performed in conscious dogs both before and after acute occlusion of a coronary artery, when endogenous sympathetic tone should be increased. In addition to hemodynamic measurements, beta-receptor blockade was assessed and plasma drug concentrations were determined after administration of these drugs.

**Methods**

Experiments were performed in 27 adult dogs of both sexes (14.5–26 kg). Silastic balloons were implanted around the left anterior descending coronary artery and the circumflex coronary artery and the attached tubes were externalized; either balloon could be inflated to produce acute myocardial infarction (19). Each dog was then studied with sterile technique 1 and 2 weeks after balloon implantation. Identical experimental protocols were used, except a coronary artery was occluded in the second experiment.

Dogs were sedated with morphine sulfate (15–20 mg, sc) and placed on their sides with limbs lightly restrained. An 8F catheter was inserted into a femoral artery and a 7F catheter was inserted into a femoral vein under local lidocaine (Xylocaine) anesthesia; the catheters were advanced with the aid of pressure monitoring and then exchanged into the left ventricle and the right atrium, respectively. A carotid artery was cannulated with another 8F catheter. All catheters were connected to Statham P23Db pressure transducers and a Brush 480 multichannel recorder to measure blood pressures. The natural frequency of the left ventricular catheter was 14 Hz. The first derivative of the left ventricular pressure (dP/dt) was measured electronically. Heart rate was calculated from electrocardiogram tracings or was recorded on a cardiotachometer. Cardiac output was measured by the indocyanine green (Cardio-Green) dye-dilution method (20). Cardiac output was divided by heart rate to yield stroke volume. Stroke work and total peripheral vascular resistance were calculated from the following formulas:

**Stroke work (g·m)**

\[
SV = \frac{P_a - P_{ra}}{Q} \times 1.052 \times 0.0136, \quad (1)
\]

**Total peripheral vascular resistance (dynes·sec·cm\(^{-5}\))**

\[
= \frac{(P_a - P_{ra})}{Q} \times 1332 \times 60, \quad (2)
\]

where SV is stroke volume (ml), \(P_a\), \(P_{ra}\), and \(P_{ven}\), are mean arterial pressure, left ventricular end-diastolic pressure, and mean right atrial pressure (mm Hg), respectively, and \(Q\) is cardiac output (ml/min).

Arterial blood pH was measured with a Radiometer PHM 71 acid-base analyzer. Cardiac beta-responsiveness was determined by measuring the heart rate response to rapid intravenous injections of isoproterenol, as described by Cleaveland et al. (21). By plotting the increases in heart rate against the doses of isoproterenol on a semilogarithmic scale a dose-response curve was constructed from which the dose required to increase heart rate 25 beats/min was determined by interpolation. This dose is referred to as the isoproterenol chronotropic dose 25 (CD\(_{25}\)).

Plasma propranolol concentration was determined by the fluorometric method of Black et al. (22) as modified by Shand et al. (23). Practolol was analyzed colorimetrically by a modified method of Fitzgerald and Scales (24). Practolol was extracted from alkalinized plasma into chloroform, hydrolyzed to the primary amine, and measured after diazo-coupling with \(N\)-naphthylethendiamine. These methods are sensitive to levels of 5–10 ng/ml of propranolol and 0.2 μg/ml of practolol.

Increasing doses of dl-propranolol, d-propranolol, and practolol\(^*\) were administered intravenously at 20-minute intervals to three separate groups of dogs after a 20–30 minute control period. These drugs were dissolved and neutralized in normal saline to a final concentration of 0.1% for both forms of propranolol and 3% for practolol. The doses administered were 0.03, 0.1, 0.3, and 1.0 mg/kg for both forms of propranolol and 0.5, 1.5, 5, 15, and 30 mg/kg for practolol. Hemodynamic measurements were taken in triplicate during the control period and 5, 10, and 15 minutes after each dose had been given; averages of the triplicate measurements are given in Results. Arterial blood was sampled 10 minutes after each dose had been administered for blood pH and plasma drug concentration. Between 15 and 20 minutes, the CD\(_{25}\) was determined. Hemodynamic parameters and plasma drug concentration were measured again 30–40 minutes after the last dose of the experimental drug had been administered.

At the end of the first study, the catheters were withdrawn and the surgical wounds were closed. The dogs were given daily injections of penicillin and streptomycin. In the second study 1 week later, the same drugs were administered to the dogs after stable left ventricular failure, as judged by the constancy of all measured hemodynamic parameters, had been produced by inflating the balloon around the left anterior descending coronary artery or the circumflex coronary artery. The presence of myocardial infarction was confirmed postmortem.

For each group of experiments, control and experimental values were compared by the \(t\)-test for paired comparisons. Differences among groups were determined

\(^*\) dl-Propranolol, d-propranolol, and practolol were supplied and chemical analyses of the drugs in the plasma were performed by Dr. R. G. Davies and his staff, Department of Clinical Pharmacology, Ayerst Laboratories, Montreal, Canada.
by analysis of variance and by comparing the slopes of the dose-response curves (25).

**Results**

**EFFECTS OF THE BETA-RECEPTOR BLOCKING AGENTS IN INTACT CONSCIOUS DOGS**

The effects of dl-propranolol, d-propranolol, and practolol in dogs before coronary artery occlusion are summarized in Tables 1 and 2. Control values were not different among these three groups of dogs, as determined by analysis of variance. Figure 1 illustrates typical responses in each group. With increasing doses of both dl-propranolol and practolol, cardiac output, stroke volume, and peak left ventricular dp/dt decreased progressively and total peripheral vascular resistance and left ventricular end-diastolic pressure increased ($P < 0.05$ in all instances). All of these changes occurred within 15 minutes after each dose was administered; some of the hemodynamic measurements returned toward control values 30-40 minutes after the last dose was given. Arterial blood pressure increased in response to the larger doses of these drugs, but neither heart rate nor arterial blood pH changed significantly.

Both dl-propranolol and practolol produced significant beta-receptor blockade, as manifested by an increase in the $CD_{25}$. The dose-response curve with respect to $CD_{25}$ for dl-propranolol was much steeper than that for practolol (Table 2). As demonstrated by Dunlop and Shanks (14), isoproterenol produced a marked fall in mean systemic arterial blood pressure in conscious dogs that were not significantly different among these three groups of dogs, as determined by analysis of variance. Figure 1 illustrates typical responses in each group. With increasing doses of both dl-propranolol and practolol, cardiac output, stroke volume, and peak left ventricular dp/dt decreased progressively and total peripheral vascular resistance and left ventricular end-diastolic pressure increased ($P < 0.05$ in all instances). All of these changes occurred within 15 minutes after each dose was administered; some of the hemodynamic measurements returned toward control values 30-40 minutes after the last dose was given. Arterial blood pressure increased in response to the larger doses of these drugs, but neither heart rate nor arterial blood pH changed significantly.

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### Table 1

<table>
<thead>
<tr>
<th>Plasma drug concentration</th>
<th>$CD_{25}$ (µg)</th>
<th>Heart rate (beats/min)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
<th>Peak left ventricular dp/dt (mm Hg/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dl-Propranolol (n = 11. 21.1 ± 0.6 kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>ND</td>
<td>2.8 ± 0.5</td>
<td>156 ± 10</td>
<td>87 ± 5</td>
</tr>
<tr>
<td>D1</td>
<td>16.4 ± 4.8*</td>
<td>7.8 ± 1.6*</td>
<td>144 ± 9</td>
<td>86 ± 6</td>
</tr>
<tr>
<td>D2</td>
<td>49.6 ± 4.9†</td>
<td>18.4 ± 4.3*</td>
<td>133 ± 9</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>D3</td>
<td>167.9 ± 15.1†</td>
<td>72.6 ± 18.9*</td>
<td>120 ± 11†</td>
<td>80 ± 7</td>
</tr>
<tr>
<td>D4</td>
<td>529.3 ± 49.2†</td>
<td>190.0 ± 33.5†</td>
<td>106 ± 10†</td>
<td>81 ± 7</td>
</tr>
<tr>
<td>R</td>
<td>281.9 ± 31.5†</td>
<td>114 ± 14</td>
<td>75 ± 6</td>
<td>125 ± 7†</td>
</tr>
</tbody>
</table>

| d-Propranolol (n = 8. 21.4 ± 2.1 kg) | | | | |
| C                        | ND             | 1.9 ± 0.4              | 162 ± 11                            | 97 ± 8                                 | 4414 ± 378                           |
| D1                       | 14.9 ± 4.6†    | 2.1 ± 0.5              | 163 ± 4                             | 95 ± 8                                 | 4289 ± 392                           |
| D2                       | 43.3 ± 6.1†    | 1.9 ± 0.4              | 167 ± 7                             | 93 ± 8                                 | 4502 ± 446                           |
| D3                       | 140.3 ± 18.1†  | 2.6 ± 0.8              | 157 ± 7                             | 92 ± 9                                 | 4210 ± 412                           |
| D4                       | 491.5 ± 77.5†  | 4.0 ± 0.9‡             | 155 ± 5                             | 92 ± 8                                 | 4336 ± 508                           |
| R                        | 280.1 ± 44.0*  | ND                     | 151 ± 8                             | 92 ± 9                                 | 4750 ± 533                           |

| Practolol (n = 8. 23.1 ± 0.8 kg) | | | | |
| C                        | ND             | 1.8 ± 0.5              | 155 ± 6                             | 85 ± 4                                 | 4584 ± 327                           |
| D1                       | 0.68 ± 0.07†   | 3.3 ± 0.6              | 149 ± 6                             | 85 ± 3                                 | 4465 ± 397                           |
| D2                       | 2.70 ± 0.22†   | 5.2 ± 1.0†             | 141 ± 8                             | 84 ± 3                                 | 4021 ± 365                           |
| D3                       | 6.96 ± 0.48†   | 6.8 ± 1.0†             | 130 ± 10                            | 83 ± 4                                 | 3681 ± 369                           |
| D4                       | 21.46 ± 1.57†  | 9.9 ± 2.0†             | 114 ± 9†                            | 82 ± 5                                 | 3012 ± 299                           |
| D5                       | 46.93 ± 3.64†  | 17.1 ± 4.4‡            | 97 ± 9‡                             | 87 ± 5                                 | 3443 ± 315                           |
| R                        | 28.77 ± 1.31†  | ND                     | 98 ± 11†                            | 75 ± 6                                 | 4750 ± 533                           |

All values are means ± SE. The numbers of experiments and body weights of the dogs are given in parentheses after each drug. Plasma concentration is given in ng/ml for both dl-propranolol and d-propranolol and in µg/ml for practolol. Measurements were made during a control period (C) prior to drug administration, after successive doses of the drugs (D1-D5), and 30-40 minutes after the last dose (R). $CD_{25}$ = isoproterenol chronotropic dose 25 and ND = not determined.

For more complete tables including values for stroke volume, left ventricular end-diastolic pressure, right atrial pressure, total peripheral vascular resistance, and arterial pH, order document no. 02409 from ASIS National Auxiliary Publication Service, Microfiche Publications, 365 East 46th Street, New York, New York 10007.

* $P < 0.01$ compared with control values.

† $P < 0.001$ compared with control values.

‡ $P < 0.05$ compared with control values.

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Regression Coefficients for Dose-Response Curves before and after Experimental Coronary Artery Occlusion

<table>
<thead>
<tr>
<th></th>
<th>d/-Propranolol Before (N = 55)</th>
<th>Practolol Before (N = 48)</th>
<th>After (N = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD50 (ng) vs. log [C]</td>
<td>58.4 ± 10.1</td>
<td>49.4 ± 11.9</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (ml/kg min⁻¹) vs. log [C]</td>
<td>-17.5 ± 4.5</td>
<td>22.2 ± 3.6</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (ml/kg min⁻¹) vs. CD50 (µg)</td>
<td>-0.20 ± 0.05</td>
<td>1.13 ± 0.56</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min) vs. log [C]</td>
<td>-11.0 ± 2.5</td>
<td>-9.6 ± 2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml) vs. log [C]</td>
<td>-3.40 ± 1.00</td>
<td>-5.75 ± 0.90</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg) vs. log [C]</td>
<td>-1.56 ± 2.95</td>
<td>-0.52 ± 1.85</td>
<td>&lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Peak left ventricular dP/dt (mm Hg/sec) vs. log [C]</td>
<td>3.85 ± 2.40</td>
<td>11.71 ± 3.14</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

All values are means ± SE. The numbers of pairs for regression analyses are given in parentheses. The statistical significance of differences between regression coefficients before and after coronary artery occlusion for each drug is indicated by a P value; no P value is given if the difference was not statistically significant. Correlation coefficients are statistically significant (P < 0.05) for all dose-response curves except heart rate vs. log [C] responses before and after coronary artery occlusion in both drug-treated groups and mean arterial blood pressure vs. log [C] responses before occlusion in dogs treated with d/-propranolol and after occlusion in dogs treated with practolol.

received practolol but not in those that received d/-propranolol.

d-Propranolol did not produce changes in any of the hemodynamic parameters measured, although it was present in the plasma in the same concentrations as its racemate after similar doses. The CD50 did not increase until the largest dose of d-propranolol was administered.

Figure 2 shows that both d/-propranolol and practolol reduced stroke work (P < 0.05 for the three largest doses) and increased left ventricular end-diastolic pressure before coronary artery occlusion, again indicating depression of left ventricular function. Neither of these changes was produced by d-propranolol.

Effects of the Beta-Receptor Blocking Agents in Dogs with Acute Myocardial Infarction

Of the 27 dogs subjected to coronary artery occlusion, 8 dogs died during ventricular fibrillation within 30 minutes of occlusion. The experimental results for the other dogs are tabulated in Tables 2 and 3. Coronary artery occlusion increased heart rate, left ventricular end-diastolic pressure, and total peripheral vascular resistance and reduced stroke volume (P < 0.05 in all instances). Cardiac output, mean arterial blood pressure, and peak left ventricular dP/dt did not change significantly. Electrocardiographic changes typical of acute myocardial infarction were demonstrated in all of the dogs, and myocardial necrosis was verified in each dog. In some dogs, acute coronary artery occlusion caused outbursts of frequent ventricular ectopic beats; this condition required injections of lidocaine (50–100 mg, iv), but no lidocaine was given during the period of experimental drug administration. One hour was allowed to elapse before experimental control values were obtained to permit cessation of spontaneous ventricular arrhythmias and disappearance of the effects of lidocaine and to ensure, by constantly monitoring heart rate and left ventricular end-diastolic pressure, that left ventricular failure was present and stabilized. During the 20–30-minute control period, there was no significant variation among the triplicate analyses of any of the hemodynamic measurements; this lack of variation indicates that the preparation had become stabilized by the time of drug administration.

Tables 2 and 3 show that both d/-propranolol and practolol caused progressive decreases in cardiac output, stroke volume, and peak left ventricular dP/dt but did not change heart rate significantly. In contrast to the pressor response prior to coronary artery occlusion (Table 1), mean arterial blood pressure tended to fall when the two drugs were administered after occlusion, but the changes were not significant. Neither agent produced significant changes in total peripheral vascular resistance, right atrial pressure, left ventricular end-diastolic pressure, or arterial blood pH. d-Propranolol did
Changes in cardiac output, plasma drug concentration, and isoproterenol chronotropic dose \( CD_{25} \) after administrations of \( dl \)-propranolol, \( d \)-propranolol, and practolol in representative experiments.

Discussion

Cardiac output and peak left ventricular dP/dt were decreased by \( dl \)-propranolol and practolol in dogs both before and after coronary artery occlusion (Tables 1 and 3). These decreases probably resulted from a reduction in myocardial contractility, because they cannot be explained on the basis of changes in heart rate or preload or afterload of the heart. Left ventricular end-diastolic pressure increased after administration of the two drugs before coronary artery occlusion (Fig. 2). Mean arterial blood pressure was increased by the drugs prior to coronary artery occlusion but was slightly reduced after occlusion (Tables 1-3). This increase in arterial blood pressure might partly account for the decreased cardiac output, but the calculated stroke work fell as left ventricular end-diastolic pressure increased (Fig. 2), again indicating that myocardial contractility was depressed. Stroke work is relatively unaffected by slight to moderate increases in arterial blood pressure such as those produced by the drugs in the present study (26, 27).

Practolol in the doses used in the present study is practically devoid of local membrane-stabilizing action (13). In addition, similar myocardial depression was not produced by \( d \)-propranolol in this study. Therefore, we concluded that the myocardial depressant effect of beta-receptor blocking agents was caused by their inhibition of endogenous sympathetic tone to the heart rather than by their quinidine-like action. There was a significant correlation \( (P < 0.05) \) between the reduction in cardiac output and the increase in \( CD_{25} \) in dogs that received either \( dl \)-propranolol or practolol before and after coronary artery occlusion (Table 2). Similarly, other investigators have shown that practolol exerts negative inotropic effects on both normal and ischemic hearts (13, 15-18), although occasional discordant results have been reported (28).

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Nakano and Kusakari (29) have reported that maximum reduction in cardiac output occurs within 15 minutes after intravenous administration of dl-propranolol. Our results also indicated that maximum decreases in cardiac output and peak left ventricular dP/dt probably occurred within 15 minutes after administration of each dose of the two active drugs, dl-propranolol and practolol. However, it is difficult to compare the reduction in myocardial contractility produced by the two drugs.

### TABLE 3

<table>
<thead>
<tr>
<th></th>
<th>dl-Propranolol (N = 6, 18.8 ± 0.5 kg)</th>
<th>d-Propranolol (N = 6, 21.1 ± 1.5 kg)</th>
<th>Practolol (N = 7, 22.9 ± 0.8 kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plasma drug concentration (µg)</td>
<td>Cardiac output (ml/kg min⁻¹)</td>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td></td>
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<td>Cardiac output (ml/kg min⁻¹)</td>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td></td>
<td>0.8 ± 0.8</td>
<td>5.0 ± 1.3</td>
<td>150 ± 11</td>
</tr>
<tr>
<td></td>
<td>D1 18.7 ± 5.1*</td>
<td>9.3 ± 2.6*</td>
<td>122 ± 8</td>
</tr>
<tr>
<td></td>
<td>D2 46.0 ± 17.9*</td>
<td>17.5 ± 3.4*</td>
<td>112 ± 8</td>
</tr>
<tr>
<td></td>
<td>D3 85.5 ± 6.7*</td>
<td>31.8 ± 6.9*</td>
<td>109 ± 9</td>
</tr>
<tr>
<td></td>
<td>D4 456.5 ± 18.4†</td>
<td>127.0 ± 31.8†</td>
<td>104 ± 10</td>
</tr>
<tr>
<td></td>
<td>R 230.3 ± 10.1‡</td>
<td>117 ± 9</td>
<td>112 ± 8</td>
</tr>
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<tr>
<td></td>
<td>0.8 ± 0.4</td>
<td>2.6 ± 0.9</td>
<td>135 ± 9</td>
</tr>
<tr>
<td></td>
<td>D1 11.8 ± 1.8†</td>
<td>2.8 ± 0.9</td>
<td>137 ± 8</td>
</tr>
<tr>
<td></td>
<td>D2 48.0 ± 4.4†</td>
<td>2.5 ± 0.9</td>
<td>137 ± 7</td>
</tr>
<tr>
<td></td>
<td>D3 157.7 ± 26.8†</td>
<td>3.2 ± 0.9</td>
<td>131 ± 6</td>
</tr>
<tr>
<td></td>
<td>D4 466.2 ± 75.8†</td>
<td>6.5 ± 0.9†</td>
<td>130 ± 6</td>
</tr>
<tr>
<td></td>
<td>R 18.5 ± 33.1†</td>
<td>ND</td>
<td>135 ± 11</td>
</tr>
</tbody>
</table>

See legend to Table 1 for explanation.

*P < 0.05 compared with control values.

†P < 0.01 compared with control values.

‡P < 0.001 compared with control values.
with respect to beta-receptor blockade, because the actual degree of blockade produced by practolol might not be measurable in the conscious dog by the isoproterenol sensitivity test. The tachycrotic response to isoproterenol in conscious dogs results from both an action of isoproterenol on the sinoatrial node and the reflex mechanism following the fall in systemic arterial blood pressure produced by the beta-agonist. Only the former action is directly related to cardiac beta-adrenergic activity. Anesthesia can obtund the reflex mechanism and thus make the heart rate response to isoproterenol depend solely on cardiac beta-receptor responsiveness (14). Practolol blocks the positive chronotropic action of isoproterenol on the sinoatrial node but does not prevent vasodilation produced by the beta-agonist. The reflex acceleration of heart rate can account for a significant portion of the isoproterenol-induced tachycardia after administration of practolol, because the inhibition of isoproterenol-induced tachycardia by practolol is potentiated by pempidine and hexamethonium, which block the reflex pathway (14, 30). Reflex tachycardia can be caused by increased sympathetic activity, decreased parasympathetic activity, or both at the sinoatrial node (31). However, since practolol in doses of less than 3 mg/kg can abolish the increase in heart rate produced by maximum stimulation of the right stellate ganglion (14), increased sympathetic activity probably was not responsible for the reflex tachycardia in the dogs given practolol. In addition, Brick et al. (30) and Barrett et al. (32) have found that atropine potentiates the inhibition of isoproterenol-induced tachycardia by practolol, suggesting that such reflex tachycardia results chiefly from cardiac vagal withdrawal.

Table 2 shows that practolol produced a greater inhibition of isoproterenol-induced tachycardia in dogs after coronary artery occlusion than it did before occlusion. This diminished tachycrotic response probably was not related to the increased heart rate during acute myocardial infarction, because the increase in heart rate produced by isoproterenol is independent of resting heart rate (14, 21). The present study also demonstrated that, although resting heart rate was not the same in all dogs, there was no significant difference in the CD10 before and after coronary artery occlusion in dogs that received either dl- or d-propranolol (Tables 1–3). Vagal tone was probably reduced during the acute phase of myocardial infarction; therefore, as with atropine pretreatment, the inhibitory action of practolol on isoproterenol-induced tachycardia was enhanced. The fact that vagal tone was withdrawn during acute myocardial infarction was supported by our finding that beta-receptor blockade did not reduce the increase in heart rate produced by coronary artery occlusion (Tables 2 and 3).

If vagal tone were absent or minimum during the acute stage of myocardial infarction, the CD10 would reflect the degree of beta-receptor blockade produced by practolol. The CD10 after administration of practolol can be compared with that after administration of dl-propranolol. Table 2 shows that, in dogs with acute myocardial infarction, the regression coefficients for the curves relating cardiac output to CD10 in groups treated with dl-propranolol and practolol did not differ significantly ($t = 1.33$, df = 68). Since the two drugs produced identical decreases in cardiac output at equivalent degrees of beta-receptor blockade, the decreased cardiac output was probably caused mainly by blockade of sympathetic stimulation at the cardiac beta-receptor site. These results are consistent with recent reports that neither dl-propranolol in doses up to 0.64 mg/kg nor practolol produce significant depression of myocardial contractility in dogs deprived of endogenous sympathetic activity (13, 33).

Dunlop and Shanks (14) have pointed out that it is difficult to assess the potency ratio of dl-propranolol and practolol for their beta-receptor blocking activity because the dose-response curve for practolol is less steep than that for dl-propranolol. The assessment of beta-receptor blockade by practolol in conscious dogs is complicated further by the reflex activation secondary to the fall in arterial blood pressure produced by isoproterenol. Dunlop and Shanks (14) have estimated that dl-propranolol is at least three or four times as potent as practolol in blocking cardiac beta-adrenergic activity. Our experiments, however, indicated that the dose-response curve with respect to CD10 after administration of practolol to dogs with acute myocardial infarction was not less steep than that after administration of dl-propranolol (Table 2). Doses of practolol as large as 15–30 mg/kg were required to reproduce the same degree of beta-receptor blockade readily accomplished by only 1 mg/kg of dl-propranolol (Table 3). Similarly large potency ratios of dl-propranolol and practolol have been reported previously by other investigators in conscious man and animals pretreated with atropine (30, 34).

The extent of cardiac depression produced by beta-receptor blocking agents is determined by preexisting cardiac sympathetic tone. Acute myocardial infarction is associated with local release of catecholamines within the myocardium (35) as well...
as with increased circulating catecholamines (36). Therefore, a major reduction in myocardial contractility would be expected if this increased sympathetic stimulation of the heart were inhibited by a beta-receptor blocking agent. Table 3 shows that cardiac output and peak left ventricular dP/dt were reduced significantly by the smallest doses of dl-propranolol and practolol administered to dogs with acute myocardial infarction, whereas larger doses were needed to produce similar effects before coronary artery occlusion (Table 1). Both cardiac output and peak left ventricular dP/dt decreased further as the doses increased under both experimental conditions; however, there was no significant difference in the regression coefficients of these dose-response curves before and after coronary artery occlusion (Table 2). Nevertheless, because left ventricular end-diastolic and systemic arterial blood pressures differed in both experimental states, the impairment of left ventricular function produced by beta-receptor blockade before and after coronary artery occlusion cannot be compared quantitatively.

Mean systemic arterial blood pressure and total peripheral vascular resistance were increased by both dl-propranolol and practolol in dogs prior to coronary artery occlusion. These increases probably were caused in part by peripheral vascular beta-receptor blockade that allowed the preexisting alpha-adrenergic activity to manifest itself. However, practolol is less than one-hundredth as potent as dl-propranolol for blocking vasodilating effects of isoproterenol (14, 30). Kayaalp and Kiran (37), on the other hand, have suggested that this pressor response to beta-receptor blockade is reflexive in origin and represents an enhanced alpha-adrenergic activity. However, the stimulus that initiates the reflex activation of alpha-adrenergic tone is not identified. This pressor response was not observed in dogs with acute myocardial infarction. The reason for this difference in the two experimental states is not entirely clear. Probably, the vascular alpha-adrenergic tone had already been activated during the acute phase of myocardial infarction and the reflex mechanism produced by beta-receptor blockade could not bring about further vasoconstriction. The small decrease in arterial blood pressure following beta-receptor blockade in dogs with acute myocardial infarction probably resulted from the associated reduction in cardiac output.

Rapid intravenous injections of practolol produced transient increases in heart rate and peak left ventricular dP/dt and decreases in left ventricular end-diastolic pressure and arterial diastolic pressure, which disappeared within 3 or 4 minutes (unpublished observation). These changes were not produced by either dl-propranolol or d-propranolol. The positive chronotropic and inotropic effects of practolol probably were caused by the sympathomimetic activity of the drug (14). Since these effects of practolol were so short-lived, they probably did not affect the more prolonged cardiodepressant action of the drug, which was caused by beta-receptor blockade.

In the present paper we have shown that dl-propranolol and practolol in the doses employed depress left ventricular function by their cardiac beta-receptor blocking activity. However, in larger doses, propranolol might exert its negative inotropic effect partly because of its quinidinelike action, as shown by Levy (8). Our study does not imply that all beta-receptor blocking agents necessarily cause myocardial depression as does dl-propranolol. Some beta-receptor blocking agents produce no significant change in left ventricular function because the myocardial depression caused by beta-receptor blockade is offset by the sympathomimetic action of these agents (8, 38).

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The Myocardial Depressant Effect of Beta-Receptor Blocking Agents: Comparative Study of dl-Propranolol, d-Propranolol, and Practolol in Awake Dogs with and Without Acute Myocardial Infarction

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