Effects of Procainamide on the Dispersion of Recovery of Excitability during Coronary Occlusion

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SUMMARY In 14 mongrel dogs, refractory periods were determined in nonischemic and acutely ischemic zones of myocardium during control conditions, 15 minutes after coronary ligation, and 10 and 20 minutes after a procainamide infusion. Following coronary ligation, refractory periods in the nonischemic area remained unchanged (100.8% of control) while in the ischemic area they decreased to 88.6% of control (P < 0.02) causing a dispersion of refractoriness of 12.2%. After the administration of procainamide, refractory periods lengthened in the nonischemic as well as in the ischemic areas, but the changes were such that the temporal dispersion caused by the coronary ligation was reduced from 12.2% to 5.5% (P < 0.01) after 10 minutes, and to 5.0% (P < 0.02) after 20 minutes of drug infusion. It is concluded that procainamide exerts different overall effects on the nonischemic and acutely ischemic canine myocardium. It is postulated that this action may play a role in the suppression of re-entrant arrhythmias.

Methods

Fourteen mongrel dogs weighing 17 to 26 kg were anesthetized with intravenous sodium pentobarbital, 30 mg/kg, intubated and mechanically respirated with a Harvard respirator. The left femoral vein was catheterized for administration of drugs and to obtain blood samples for determination of procainamide levels, and the aortic pressure monitored via a catheter introduced in the left femoral artery, using a Statham P23Db transducer. After induction of complete heart block by injecting 0.2 ml of formaldehyde in the septum in the area of the bundle of His, heart rate was kept constant at a basic cycle length (S1-S1) of 500 msec by right ventricular pacing using a S-88 Grass stimulator. Four pairs of fine stainless-steel, Teflon-coated plunge electrodes (0.003 inch diameter) were inserted into the left ventricular myocardium, two pairs in an area subserved by the left anterior descending coronary artery that subsequently was made ischemic and the other two pairs in an area with intact coronary blood flow. Premature stimuli (S2) were introduced in each left ventricular zone through a pair of stimulating electrodes and a pair of sensing electrodes was placed at a distance of 5–8 mm.
Bipolar electrograms from the intramyocardial electrodes (frequency response 40–500 Hz), standard electrocardiogram Lead II and aortic pressure were simultaneously recorded using an Electronics for Medicine recorder at paper speeds of 100 mm/sec. The refractory periods of ventricular muscle in the nonischemic and ischemic areas were determined by the introduction of premature stimuli. The R-R interval was scanned by delivering a test impulse every eighth paced beat, using pulses of two times diastolic threshold and 2 msec duration. The refractory period was defined as the longest R-to-stimulus (R-S2) interval that did not result in locally propagated response.18 The potential limitation in measurements employing this method is less than 5 msec.

Because in some experiments there were differences between refractory periods in the normal and potentially ischemic areas during control measurements, relative changes in refractory periods were determined and then compared, using the formula:

\[ \% \Delta \text{RP} = \frac{\text{RP}_2 - \text{RP}_1 \times 100}{\text{RP}_1} \]

where refractory periods (RP) 1 and 2 refer respectively to measurements during control conditions and after interventions.

After obtaining control values of the refractory periods in both the nonischemic and the potentially ischemic areas, myocardial ischemia was produced by ligating the left anterior descending coronary artery distal to the first diagonal branch. The ischemic area showed rapid development of cyanosis and paradoxical motion. Measurements were repeated after 15 minutes of coronary ligation, at a time when these parameters were stable. Following these measurements while maintaining coronary ligation, procainamide (Pronestyl) was infused intravenously 2 mg/kg/min for five minutes (total dose 10 mg/kg) and the repeat measurements were obtained 10 and 20 min after the start of drug administration. Each set of recordings required approximately 2–3 min.

Serum procainamide concentrations were determined from blood samples obtained before each set of measurements was undertaken. The dose given (10 mg/kg) has been frequently used as a bolus in experimental studies, but we chose to administer it over 5 min to avoid some of the hemodynamic disturbances that have been previously reported.4–15

Statistical significance was determined by using the t-test for paired data.

**Results**

The mean serum procainamide levels were 9.2 ± 2.7 μg/ml at 10 min and subsequently levels declined to a mean of 7.2 ± 0.4 μg/ml at 20 min following initiation of drug administration and to 5.0 ± 0.5 μg/ml at 30 min after start of drug infusion. Although in this study we did not attempt to achieve a steady state drug concentration, the procainamide levels were within the range considered therapeutic throughout the experiment.8

During control conditions refractory periods in the nonischemic and potentially ischemic areas were similar (table 1). Following coronary ligation, refractory periods in the nonischemic area remained essentially unchanged, 100.8 ± 1.7% of control (mean ± SEM), while in the ischemic area they decreased by 11.4% to 88.6 ± 3.8% of control (P < 0.02), causing a mean dispersion of 12.2% in the refractory periods (fig. 1). Ten minutes after the start of procainamide administration, refractory periods lengthened in both the nonischemic and the ischemic areas, to 107.8 ± 2.3% of control in the nonischemic area (P < 0.02) and to 102.3 ± 4.9% of control in the ischemic area (P < 0.005); these changes were such that the mean tem-

![Figure 1. Refractory periods after 15 min of coronary occlusion and procainamide. Coronary occlusion resulted in a dispersion of refractory periods of 12.2% that was decreased to 5.5% (P < 0.01) after 10 min and to 5.0% (P < 0.02) after 20 min of procainamide infusion.](http://circ.ahajournals.org/)

**Table 1. Changes in Refractory Periods Following Ischemia and Procainamide Administration**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Post occlusion</th>
<th>10 min Post PA</th>
<th>20 min Post PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonischemic area</td>
<td>154.2 ± 8.5</td>
<td>155.8 ± 9.5</td>
<td>166.6 ± 9.9</td>
<td>162.5 ± 9.2</td>
</tr>
<tr>
<td>Ischemic area</td>
<td>152.5 ± 11.2</td>
<td>135.8 ± 12.4</td>
<td>155.8 ± 12.9</td>
<td>153.3 ± 14.3</td>
</tr>
</tbody>
</table>

Values are mean ± SEM (in msec).

PA = procainamide.
poral dispersion of refractoriness decreased from 12.2% to 5.5% ($P < 0.01$) (fig. 1). A similar effect was present 20 min after procainamide administration, prolonging the refractory periods in the nonischemic area to 105.1 ± 0.9% of control ($P < 0.02$) and to 100.1 ± 4.5% of control in the ischemic area ($P < 0.01$), thereby decreasing slightly further the mean temporal dispersion to 5.0% ($P < 0.02$) (fig. 1).

The aortic pressure remained stable during the experimental procedures, with small changes observed during procainamide administration that reverted to control values within a few minutes.

**Discussion**

This study indicates that procainamide prolongs refractory periods in both the ischemic and the nonischemic myocardium. The extent of this action on ventricular refractoriness was such that relative changes in the ischemic area were greater than those in the nonischemic area and served to decrease the dispersion of refractory periods between the two areas. After coronary occlusion a disparity of 12.2% between the two areas became apparent, but was significantly decreased by procainamide to 5.5% ($P < 0.01$) after 10 min and to 5.0% ($P < 0.02$) after 20 min of its administration (fig. 1).

Wiggers et al. and Han have demonstrated that the ventricular vulnerability to fibrillation increases after acute coronary occlusion. It has also been shown that following coronary occlusion there is an increase in the dispersion of recovery of excitability in the ischemic ventricle. Presumably, the nonuniformity of duration of refractory periods favors the fractionation of wave fronts and makes re-entrant activity more likely to occur, thus providing the electrophysiological basis for the decreased stability of the ischemic myocardium. Then any intervention, physiological or pharmacological, that decreases the dispersion of refractory periods diminishes the likelihood of re-entrant arrhythmias.

Previous studies have shown that procainamide decreases excitability and prolongs the effective refractory period of ventricular muscle. More recently, microelectrode studies have demonstrated that procainamide decreases automaticity and increases the effective refractory period in Purkinje fibers. Yoon et al. have also shown that procainamide makes the acutely ischemic ventricle less vulnerable to fibrillation. Our results complement those findings by showing that changes in the ischemic myocardium parallel those in the nonischemic muscle, although they are of different magnitude. The basis for the variability in responses is not known. The possibility of differential drug distribution in the two zones has to be considered, although it is more likely that local morphologic and metabolic changes in the ischemic zone could play a role.

It should be noted that the determination of refractory periods in the intact heart is the result of a complex series of events and is only an approximation of the value that could be established from determinations in individual cells. However, if the increased asynchrony of the ischemic myocardium with respect to recovery plays a role in the initiation of re-entrant arrhythmias, the homogenizing effect of procainamide on the dispersion of refractory periods could explain the beneficial effects of the drug in suppressing arrhythmias of re-entrant origin and restoring the electrical stability of the ischemic myocardium.

**References**

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R Levites, J I Haft, J Calderon and Venkatachalapathy

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