Electrophysiologic Effects of Coronary Occlusion and Reperfusion

Observations of Dispersion of Refractoriness and Ventricular Automaticity

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SUMMARY
In order to determine the electrophysiologic changes that occur during coronary occlusion and following reperfusion, 19 mongrel dogs were studied. Refractory periods were determined by the extrastimulus method in nonischemic and ischemic zones prior to and after variable periods of left anterior descending artery occlusion and reperfusion. After 15-30 minutes of occlusion, refractory periods in the nonischemic zones remained unchanged while in the ischemic zone they shortened by 17%, resulting in a dispersion of refractoriness. Within three minutes of reperfusion, arrhythmias appeared together with a marked directional change of refractory periods to a prolongation by 34% (P < 0.001) in the ischemic zone and by 3% (P < 0.02) in the nonischemic zone. Refractory periods returned to baseline values after 60 minutes of reperfusion. After 60-90 minutes of occlusion, refractory periods in the nonischemic zones were unchanged whereas in the ischemic zone they demonstrated a decrease by 28% (P < 0.001), again resulting in a dispersion of refractoriness. Within five minutes of reperfusion, refractory periods in the ischemic zone prolonged by 44% (P < 0.001). Similar but smaller directional changes were also seen in nonischemic zones. Concomitant with the observed prolongation in refractory periods frequent ventricular ectopic activity was again documented. In addition, refractory periods did not return to control values after periods of observation up to 120 minutes in this group. In seven dogs, complete heart block was induced to ascertain the rate of idioventricular pacemaker and the effect of ventricular override on the escape interval. Control ventricular rates (53.3 ± 5.7 beats/min) remained unchanged (52.3 ± 5.6) following coronary occlusion, but decreased to 48.0 ± 4.4 (P < 0.05) during reperfusion. Mean control escape intervals (1.8 ± 0.2 sec) did not change after occlusion (1.7 ± 0.2 sec) but prolonged to 2.1 ± 0.2 sec (P < 0.05) following reperfusion. In conclusion: 1) sudden prolongation in refractory periods following reperfusion leads to an overshoot resulting in a dispersion of refractoriness temporally related to the onset of ventricular arrhythmias and 2) re-entry, and not enhanced automaticity, appears to be the mechanism for postperfusion arrhythmias.

Although the appearance of ventricular arrhythmias during experimental coronary occlusion has been extensively studied, frequently seen but less often commented upon is the phenomenon of ventricular ectopic activity following release of a previously ligated coronary artery. In the 1930s Tennant and Wiggers1 reported a high incidence of ventricular arrhythmias after the sudden restoration of blood flow to an occluded coronary artery in canine experiments. Similar findings have been reported by others.2-7

With the advent of coronary bypass surgery, these experimental observations have gained importance in the clinical setting. Some reports have indicated that coronary bypass surgery can be effective in the treatment of refractory ventricular arrhythmias.8-10 However, a recent preliminary study suggested that coronary bypass may actually increase the incidence of exercise-induced arrhythmias.11 The electrophysiologic effects of coronary reperfusion have not been adequately studied. This investigation was therefore undertaken to examine the effect of coronary occlusion and reperfusion on ventricular refractoriness and automaticity.

Methods

Studies were carried out in 19 mongrel dogs weighing 20 to 25 kg. Pentobarbital anesthesia (30 mg/kg i.v.) was administered and the animals were ventilated with room air using a Harvard Respirator via a cuffed endotracheal tube. After performing a mid-line thoracotomy, the heart was suspended in a pericardial cradle and heart rates controlled by right atrial pacing after destroying the sinus node with a 0.1 ml injection of formaldehyde.

Four pairs of fine Teflon-coated stainless steel plunge electrodes (0.003 inch diameter) were inserted into the left
ventricular myocardium, two in each nonischemic and potentially ischemic zone, using techniques previously described.12, 13 In each zone the pair of sensing electrodes was placed at a distance of 5-8 mm from the pair of stimulating electrodes. Bipolar electrograms (frequency response 40-500 Hz) from the intramyocardial electrodes, standard ECG lead II and blood pressure (obtained via an aortic catheter introduced through a carotid artery using a P23Db transducer) were simultaneously recorded using an Electronics for Medicine oscilloscopic recorder at paper speeds of 50 and 100 mm/sec.

Refractory periods were determined using the extrastimulus method by scanning the R-R interval.14, 15 The stimulus intensity was two times above diastolic threshold. The test impulse was of 2 msec duration and was delivered every eight basic cycles. The stimuli were started late in the cardiac cycle and moved progressively earlier by 5 msec decrements. The refractory period was defined as the longest R-to-stimulus interval that did not result in a propagated response (fig. 1). Because in most experiments there were minor differences between refractory periods in the nonischemic and potentially ischemic zones during control measurements, absolute as well as relative changes in refractory periods were determined and compared using the formula:

\[
\frac{\% \Delta \text{refractory period}}{= \frac{\text{refractory period } 2 - \text{refractory period } 1 \times 100}{\text{refractory period } 1}}
\]

where refractory periods 1 and 2 refer respectively to measurements during control conditions and after interventions. Refractory periods were determined during control conditions, at the end of 15-30 minutes or 60-90 minutes of left anterior descending coronary artery occlusion, and following periods of reperfusion of up to 120 minutes.

In seven dogs, complete heart block was produced by injecting 0.2-0.4 ml of formaldehyde into the area of the bundle of His.14 The rate of the idioventricular pacemaker16 and the effects of sudden termination of 30 sec of rapid ventricular pacing17 at 120 beats/min on the time for a ventricular escape to occur were determined before and 15 min after coronary ligation and following reperfusion, and were used as indices of ventricular automaticity.16, 17

All experiments in which ventricular fibrillation developed were excluded. Each dog served as its own control and statistical significance was determined using Students' t-test for paired values.

Results

I. Refractory Periods

15-30 Minute Occlusions

Control refractory periods in nonischemic and potentially ischemic zones were similar (table 1). Following coronary occlusion, refractory periods in the nonischemic zones remained essentially unchanged while in the ischemic zone, they shortened by 16.9 ± 3.7% to 83.1% of control (P < 0.005),
resulting in a dispersion of refractoriness (fig. 2). Within three minutes of reperfusion marked directional changes of refractory periods were observed. Ischemic zone refractory periods prolonged by 34.4% resulting in an overshoot to 17.5 ± 1.8% above control values \((P < 0.001)\). Small but significant changes were seen in nonischemic zones as well, where refractory periods prolonged by 3% to 3.7 ± 0.9% above control values \((P < 0.02)\) (fig. 2). These overshoot prolongations in refractoriness were temporally related to the appearance of ventricular ectopic activity and could be documented within one minute of reperfusion when the presence of ventricular arrhythmias did not preclude such measurements at that time.

Ischemic zone refractory periods were 10.8 ± 1.9% above control values \((P < 0.001)\) after 15 minutes and 6.9 ± 2.6% above control \((P < 0.05)\) after 30 minutes of reperfusion. Within 60 minutes of reperfusion all measurements had returned to baseline values.

60-90 Minute Occlusions

Control nonischemic and potentially ischemic zones had similar refractory periods (table 1). With 60-90 minute coronary occlusions, refractory periods in the nonischemic area were unchanged whereas in the ischemic area they demonstrated a significant decrease by 28.0 ± 3.0% to 72.0% of control \((P < 0.001)\), again resulting in a dispersion of refractoriness (fig. 3). Within five minutes of reperfusion, ischemic zone refractory periods prolonged by 44.7% to 16.7 ± 3% above control values \((P < 0.001)\). Similar directional changes but of lesser magnitude were also seen in the nonischemic areas (fig. 3). During this early period of reperfusion and concomitant with the observed overshoot prolongation in refractory periods, marked ventricular ectopic activity was again invariably documented.

Refractory periods in ischemic zones were 13.3 ± 3.0% above control \((P < 0.005)\) after 15 minutes of reperfusion, 11.8 ± 3.2% above control \((P < 0.02)\) after 30 minutes and remained elevated at 8.7 ± 2.7% above control \((P < 0.01)\) after periods of observation up to 120 minutes (fig. 3). Smaller but significant changes also persisted in nonischemic areas (fig. 3).

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**Table 1**

<table>
<thead>
<tr>
<th>Duration of occlusion</th>
<th>Control (NI)</th>
<th>Ischemic (Is)</th>
<th>Post occlusion</th>
<th>Post-reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 – 30 min</td>
<td>NI 116±4.1</td>
<td>Is 121±3.9</td>
<td>NI 100±6.5</td>
<td>Is 120±7.8</td>
</tr>
<tr>
<td></td>
<td>± 1.2</td>
<td>± 0.5</td>
<td>± 1.0</td>
<td>± 1.2</td>
</tr>
<tr>
<td>60 – 90 min</td>
<td>NI 120±7.8</td>
<td>Is 124±8.5</td>
<td>NI 86±7.2</td>
<td>Is 86±7.2</td>
</tr>
<tr>
<td></td>
<td>± 1.2</td>
<td>± 0.5</td>
<td>± 1.0</td>
<td>± 1.2</td>
</tr>
<tr>
<td></td>
<td>4.1</td>
<td>3.9</td>
<td>4.6</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* msec; mean ± SEM.

Abbreviations: NI = nonischemic zone; Is = ischemic zone.

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**Figure 3**

Refractory periods 60-90 minutes after occlusion and reperfusion \(N=10\) dogs. Ischemic zone refractory periods decreased by 28% after coronary occlusion and prolonged by 44% following reperfusion. Smaller changes are also seen in the nonischemic area. Note that the measurements do not return to control values after 120 minutes of reperfusion.
II. Ventricular Automaticity

After inducing complete heart block, the control rate of the idioventricular pacemaker was 53.3 ± 5.7 beats/min. Following coronary occlusion, the ventricular rates remained essentially unchanged (52.3 ± 5.6 beats/min) but decreased to 48 ± 4.4 beats/min during the first 3-5 minutes of reperfusion (fig. 4). Idioventricular rates after reperfusion were significantly slower than control (P < 0.05) but not different from those observed during ischemia.

The mean control escape intervals after cessation of ventricular overdrive were 1.8 ± 0.2 seconds and did not change after occlusion (1.7 ± 0.2 seconds), but prolonged slightly though significantly to 2.1 ± 0.2 seconds (P < 0.05) following reperfusion (fig. 4).

Discussion

Since Tennant and Wiggers' first noted ventricular irritability during sudden restoration of coronary blood flow forty years ago, several reports have corroborated their findings. However, few studies have attempted to determine the basic electrophysiologic mechanisms responsible for these arrhythmias. The advent of coronary bypass surgery has made these observations relevant to the clinical setting. Some recent reports have suggested that saphenous vein bypass surgery alone, or in combination with other surgical interventions, can be an effective mode of therapy for refractory ventricular arrhythmias. However, a recent preliminary study in a randomized group of patients has shown that the incidence and/or severity of exercise-induced ventricular arrhythmias may actually increase after bypass surgery.

The present study clearly shows marked directional changes in ischemic zone refractory periods after coronary reperfusion (figs. 2 and 3). The marked and sudden prolongation in refractory periods in this area
led to a dispersion of refractoriness that was temporally related to the onset of severe ventricular arrhythmias. Ventricular arrhythmias are generally believed to be due to re-entry or enhanced automaticity.12, 18 Wiggers,19 Han,18 and others12, 16 have postulated that increased dispersion of refractoriness during coronary occlusion can cause fractionation of wave fronts and lead to re-entrant arrhythmias. In a similar manner, it can be postulated that the dispersion of refractory periods that follows reperfusion might lead to re-entry and thus be the mechanism for reperfusion arrhythmias. Our observations of an actual decrease in ventricular automaticity following reperfusion (fig. 4), at the time when ventricular irritability was marked, further strengthens the probability of a re-entry mechanism.

These data are consistent with the in vitro findings of Trautwein and Dudel,20 who described shortening of the duration of action potential during hypoxia and transient overshoot prolongation of action potential duration during recovery. Similarly, Bing et al.21 reported shortening of the Q-T interval on epicardial electrogams during coronary occlusion and transient Q-T interval prolongation following release of the ligature. Changes in the duration of action potential and Q-T intervals frequently parallel changes in refractoriness.23 While the experimental conditions in the present study were different, changes in refractory periods were directionally similar to the observations on action potentials and Q-T interval previously reported. However, in a recent preliminary report,24 a further decrease was found in refractory periods following reperfusion. The reasons for the discrepancy with the present findings are not clear but could be due to differences in protocols, since these investigators instituted reperfusion after very short occlusions (less than 15 min) while pacing at higher rates.

The time course of changes in refractoriness following reperfusion is of interest. The electrophysiologic changes observed after 15-30 minutes of occlusion reverted to normal within 60 minutes of reperfusion (fig. 2). However, when periods of occlusion were prolonged to 60-90 minutes before reperfusion, only an incomplete recovery was apparent after two hours of reperfusion (fig. 3). Lang and co-workers24 have documented a sudden washout of metabolites, notably lactic acid and potassium, following reperfusion. Thus, reperfusion may cause a sudden change in the electrolyte environment which could explain some of the electrophysiologic changes in ischemic as well as nonischemic zones observed in the present study. Similarly, the decrease in ventricular automaticity that follows reperfusion might be due to an increased concentration of potassium extracellularly leading to a reduction of the intracellular to extracellular potassium gradient.28

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