the plot of source resistance fall precisely on a straight line these assumptions are likely to be true. The values of the correlation coefficients presented in Table 1 do suggest that in most cases a straight line fits the data well. However, the degree of linearity seems to vary between hearts. Sometimes a slightly curved line seems to fit the results better than a straight line. Two extreme examples, measured for two different hearts, are shown in Figure 9. When a more curved relationship is found it is always in the direction shown in Figure 9. This sort of curvature is in agreement with the observation of Bergel (discussion of Elzinga and Westerhof) that the predicted mean hydromotive pressure obtained by extrapolation is greater than the measured mean hydromotive pressure determined from an isovolumic beat. The cause of this is not yet clear to us. However, in a physiological working range (mean left ventricular pressure of 50–70 mm Hg and mean aortic flow of 2–5 cm³/sec) a linear approach seems to be reasonable.

In conclusion we would like to state that the source impedance concept appears to be a useful tool to describe the pumping ability of the heart in quantitative terms. Occlusion of a part of the coronary arterial system affects the hydromotive pressure but not the source resistance. The pumping ability of the left heart can, after infarction, be restored almost completely by an increase in left atrial filling pressure. The Frank-Starling mechanism which the heart can use to compensate for the effects of a loss in contractile tissue therefore seems to be very effective in this situation.

Acknowledgments

We thank I.T. Gabe, C.J. Mills, and M.I.M. Noble for the stimulating discussions on the concept of source impedance.

References


Electrophysiological and Antiarrhythmic Effects of Propranolol in Canine Acute Myocardial Ischemia

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SUMMARY To correlate the antiarrhythmic and electrophysiological effects of propranolol in acute myocardial ischemia, we examined the effects of temporary (15-minute) ligations of the left anterior descending coronary artery in studies on 15 dogs. We recorded bipolar electrograms and monophasic action potentials from the ischemic and normal zones and measured the intervals from the onset of QRS in a standard electrocardiogram lead to the major deflection of electrograms recorded from the ischemic and normal zones. We also determined monophasic action potential duration (APD) and effective refractory period (ERP). Data for control ligations were compared to those during which propranolol, 40 μg/kg, was administered intravenously immediately after ligation. Propranolol reduced the mean number of ventricular beats per minute (from 15 to 6) (P < 0.01). Propranolol slowed conduction in the ischemic zone (by 10 msec at peak effect, P < 0.01) and had no or only a very slight effect (by 1-msec at 15 minutes, P < 0.05) on conduction in the normal zone. Propranolol also prolonged APD in the ischemic (32-msec) and normal (14-msec) zones (P < 0.01), prolonged ERP in the ischemic (41-msec) and normal (28-msec) zones (P < 0.01), and reduced the APD/ERP ratio in the ischemic (1.62 to 1.47) (P < 0.01) and normal (1.62 to 1.55) (P < 0.05) zones. During the control ligation, APD in the ischemic zone was 25 msec shorter than in the normal zone (P < 0.01), but with propranolol the difference was not significant. The effects of propranolol in slowing conduction in the ischemic zone, in prolonging refractoriness, in reducing APD/ERP, and in reducing the disparity in APD between ischemic and normal zones may explain its demonstrated antiarrhythmic effects in acute myocardial ischemia.

SPECULATION on the mechanism of action of antiarrhythmic drugs is based in large measure on microelectrode studies of normal, isolated cardiac tissue. In these studies, the effects of an agent on various parameters including conduction, action potential duration, and refractory period are determined and the results are extrapolated to the arrhythmic, abnormal heart in situ. However, there are limitations to this method because the effects of antiarrhythmic drugs on the electrophysiological properties of normal
isolated cardiac tissue may differ from their effects on normal and abnormal tissue in situ. These limitations may be of particular importance in the case of β-adrenergic blockade because isolated cardiac tissue has been separated from its connection with the autonomic nervous system and from exposure to circulating catecholamines. Thus the effects of β-adrenergic blockade are mediated entirely by blockade of the effects of intrinsic stores of catecholamines, the importance of which may not be great.

In our present study we examined the electrophysiological effects of racemic propranolol, which has both β-adrenergic and local anesthetic properties, on canine acute myocardial ischemia. We used a technique of paired, 15-minute periods of coronary artery ligation (associated with reversible structural, histochemical, and electrophysiological effects) to determine the actions of propranolol on conduction, action potential duration and refractory period in the ischemic and normal zones of the heart. In this experimental model, ventricular arrhythmias commonly occur, so that we could determine the antiarrhythmic effects of propranolol against ventricular arrhythmias and directly correlate this property with underlying electrophysiological effects.

Methods

In adult mongrel dogs anesthetized with pentobarbital (30 mg/kg, iv) and mechanically ventilated, the heart was exposed through a midsternal thoracotomy. Silver electrodes embedded in acrylic plaques were sewn to the right atrium, the lateral right ventricular epicardium, and the left ventricular epicardium in the distribution of the left anterior descending coronary artery. A suction electrode, which consisted of silver wire placed within polyethylene tubing, also was placed on the lateral right ventricular epicardium. A ligature in the form of a sling was placed around the left anterior descending coronary artery distal to the first or second diagonal branch so that repeated ligations and releases could be performed. The sinus node was excised.

The protocol for the study was as follows: A control ligation of the left anterior descending coronary artery was maintained for 15 minutes. The atria were paced through bipolar electrodes at constant R-R intervals, ranging from 450 to 550 msec among dogs, and the electrocardiogram (ECG) was recorded continuously. Bipolar electrograms were recorded from the normal zone in the right ventricle and from the ischemic zone between filter frequencies of 12–500 Hz for the 15 minutes of ligation and for 15 minutes after the ligation was released. Monophasic action potentials were recorded from the ischemic and normal zones after 15 minutes of coronary artery ligation between filter frequencies of 0.1–500 Hz by means of epicardial electrodes in the ischemic zone and the suction electrode in the normal zone.

One hour after the above recordings had been made, the coronary artery was ligated again. Immediately after ligation racemic propranolol (40 μg/kg) was administered through a vein in the forelimb. In four dogs propranolol was administered with the first ligation, and control ligations were performed 31/2 hours later. The results for these dogs were similar to and not significantly different from those obtained for dogs in which control ligations were performed first. The data from all dogs were grouped.

During each ligation, we measured the number of ventricular beats occurring per minute for all but the first 2 minutes. Intervals (Q-EG) were measured from the initial deflection in the QRS complex of the limb lead to the major deflection of the bipolar electrograms in the ischemic and normal zones. Intervals from the atrial stimulus artifact to the onset of the QRS (S-R) also were measured. Monophasic action potential duration (APD), which has been shown to reliably reflect the action potential duration which would be recorded with intracellular microelectrodes in the same vicinity, was measured for the ischemic and normal zone after 15 minutes of coronary artery ligation. The effective refractory period (ERP) was also determined after 15 minutes of ligation by means of a programmed premature stimulus of 2 times diastolic threshold delivered after every 10th atrial paced beat. Measurements were made with a standard error of ± 1 msec.

If ventricular fibrillation occurred during the control ligation or the ligation during which propranolol was administered, the study could not be completed and data for these dogs were not included in the results. When ventricular fibrillation occurred after release of the ligature and successful electroconversion was performed with a single shock of 50 J or less, data for the dogs were included in the study. The coronary artery was ligated in 23 dogs. Of these, 15 form the basis of the present report. Ventricular fibrillation occurred after release of the control ligation or with drug administration, or both, in four of these dogs. The remaining eight dogs were not included in the study because of the occurrence of ventricular fibrillation during ligation.

To evaluate statistical significance, we used the paired Student's t-test in which control determinations were paired with values obtained from the same dog during the ligations in which propranolol was administered.

Results

Within a few minutes after control coronary artery ligation, there was discoloration of cardiac tissue and a monophasic potential was recorded in the zone supplied by the ligated artery. Within 5 minutes, there was significant delay in activation of tissues in the ischemic zone (Table I). In addition, ventricular beats occurred, the frequency of which generally reached a peak between 5 and 10 minutes. After administration of propranolol, the number of ventricular beats per minute which occurred during ischemia declined from a mean of 15 ± 6 (SE) for control ligations to a mean of 6 ± 2 (P < 0.01) (SE of difference = 2.5). While it exerted this antiarrhythmic effect, propranolol had the following effects on electrophysiological parameters. Figure 1 shows an example of the effects of propranolol on conduction intervals in the ischemic and normal zones. In Figure 1A are recordings made during the control ligation and in 1B, those made after propranolol administration; both sets of records were obtained 15 minutes after coronary artery ligation. During the control ligation the Q-EG interval in the ischemic zone was 54 msec, whereas with propranolol this interval increased to 72 msec. The corresponding Q-EG interval in the normal zone was 44 msec.
The interval from the atrial stimulus artifact (S) to the onset of QRS complex to major deflection of local electrograms complex. During the control ligation (A) the intervals from the coronary artery. The vertical line shows the onset of the QRS complex, and the bottom trace (NL) shows electrograms from the normal zone 15 minutes after ligation of the left anterior descending coronary artery. The vertical line shows the onset of the QRS complex. During the control ligation (A) the intervals from the onset of QRS complex to major deflection of local electrograms (Q-EG) were 54 msec for the ischemic zone and 44 msec for the normal zone. The interval from the atrial stimulus artifact (S) to the onset of the QRS complex (S-R) was 99 msec. During the ligation in which propranolol was administered (B), the Q-EG intervals were 72 msec for the ischemic zone and 43 msec for the normal zone; S-R interval was 143 msec.

During the control ligation and 43 msec with propranolol and thus virtually the same. The S-R interval, representing atrioventricular (AV) conduction, was increased by propranolol from 99 to 143 msec.

Figure 2 and Table 1 show the effects of propranolol on S-R and Q-EG intervals for the ischemic and normal zones. S-R intervals were not significantly changed during control ligations, but with propranolol the mean S-R intervals were increased by 14-20 msec (P < 0.01) during the 30-minute period of the study, with peak effect appearing at 15 minutes. This prolongation of AV conduction, a well-established effect of propranolol,14, 15 indicates in an indirect manner that a degree of β-adrenergic blockade occurred in our study. Similar doses of propranolol in other studies on canines14 and also on humans15 have caused a similar prolongation of AV conduction during atrial pacing.

The middle panel of Figure 2 shows the effects of propranolol on Q-EG intervals in the ischemic zone. During control ligations, there was a mean prolongation of 6-7 msec in Q-EG intervals in the ischemic zone, and this measurement returned to preligation values within 5 minutes after release of the ligature. With propranolol, Q-EG intervals in the ischemic zone were further prolonged by a mean of 12-16 msec (P < 0.01), with a peak difference of 10 msec between propranolol and control at 15 minutes. After release of the ligature, Q-EG intervals in the ischemic zone rapidly declined and within 5 minutes were not significantly different from those measured after release of the control ligation; this was so even though the S-R interval remained prolonged, indicating a continuing effect of propranolol on AV conduction.

In the normal zone, Q-EG intervals were not significantly changed during the control ligation. With propranolol, in contrast, these intervals were prolonged by 1 msec at 15 minutes after coronary artery ligation; this difference was statistically significant at the 5% level. The importance of this slight change in Q-EG intervals of the normal zone is unclear because the difference was at the limits of the standard error of measurement. However, it may indicate a very slight effect of propranolol in slowing conduction in normal cardiac tissue. As shown in Table 1, QRS duration was not significantly changed by the dose of propranolol used.

Table 2 and Figure 3 show the effects of propranolol on APD and ERP in the ischemic and normal zones. In the ischemic zone, propranolol prolonged APD by 32 msec (P < 0.01) and ERP by 41 msec (P < 0.01). In the normal zone, propranolol had similar but less marked effects, prolonging APD by 14 msec (P < 0.01) and ERP by 20 msec (P < 0.01). The greater magnitude of the effect of propranolol on APD in the ischemic zone had one important consequence. During the control ligation, APD in the ischemic zone was 25 msec less than that in the normal zone (P < 0.01), but with propranolol this disparity was reduced to 7 msec (not significant).

Table 2 and Figure 4 show the effect of propranolol on the ratio of APD to ERP for the ischemic and normal zones. This ratio was reduced by propranolol from 1.62 to 1.47 (P < 0.01) in the ischemic zone and from 1.62 to 1.55 (P < 0.05) in the normal zone.

Discussion

In the present study propranolol exerted an antiarrhythmic action by reducing the frequency of ventricular beats during acute myocardial ischemia; this effect is similar to that of sympathectomy.16 At the time propranolol exerted...
this effect the concomitant effects on electrophysiological properties of both ischemic and normal zones were determined. Propranolol slowed intraventricular conduction in the ischemic zone, had no or only a very minimal effect (at this effect the concomitant effects on electrophysiological

TABLE 2 Effects of Propranolol on Monophasic Action Potential Duration (APD), Effective Refractory Period (ERP), and APD/ERP in the Ischemic and Normal Zones

<table>
<thead>
<tr>
<th>Control ligation</th>
<th>Propranolol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ischemic zone</strong></td>
<td></td>
</tr>
<tr>
<td>APD (msec)</td>
<td>238 ± 3*</td>
</tr>
<tr>
<td>ERP (msec)</td>
<td>147 ± 5</td>
</tr>
<tr>
<td>APD/ERP</td>
<td>1.62 ± 0.04</td>
</tr>
<tr>
<td><strong>Normal zone</strong></td>
<td></td>
</tr>
<tr>
<td>APD (msec)</td>
<td>263 ± 3</td>
</tr>
<tr>
<td>ERP (msec)</td>
<td>159 ± 5</td>
</tr>
<tr>
<td>APD/ERP</td>
<td>1.62 ± 0.03</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SE.
* P < 0.01, ischemic vs. normal.
† P < 0.01, control vs. propranolol.
‡ P < 0.05, control vs. propranolol.

In microelectrode studies on normal isolated cardiac tissue, propranolol's effects were shown to depend in part on the concentration of drug used. In studies on Purkinje fibers and ventricular muscle, propranolol had no effect or, in higher concentrations, it reduced the rate of rise of phase 0 of the action potential. This parameter is thought to correlate with the rate of conduction of an impulse. Also, although propranolol shortened APD and ERP of Purkinje fibers, it had no effect on or, in higher concentrations, it prolonged these parameters in ventricular muscle.

Thus, since propranolol reduced the rate of rise of phase 0 and prolonged ventricular APD and ERP only in high concentrations, a potentiation of these effects could cause the greater slowing of intraventricular conduction and greater prolongation of ventricular APD and ERP in the ischemic zones which we have found in studies on the heart in situ. On the other hand, there also could have been a peculiar and altered response of ischemic tissue to propranolol. In addition, it is not clear whether the observed effects of propranolol were due to β-adrenergic blockade (β-propranolol) or local anesthetic actions (d-propranolol), since slowing of intraventricular conduction and prolongation of ventricular APD and ERP, as well as antiarrhythmic actions, can be caused by either mechanism.

Several factors might potentiate or otherwise alter either the local anesthetic or β-adrenergic blocking properties of
propranolol in ischemic tissue. Local levels of extracellular potassium are elevated in the ischemic zone and this potentiates local anesthetic properties. Metabolites released from cells in the ischemic zone, or an alteration in the enzymatic activity of ischemic cells, could modify the effects of propranolol. Different local concentrations of catecholamines in the ischemic zone might cause the β-adrenergic blocking properties of propranolol to differ.

Another factor may be an interaction between the effects of propranolol and catecholamines on the resting transmembrane potential of ischemic tissue. Delay in conduction during ischemia is due in part to a reduced rate of change of phase 0 of the action potential. In depressed tissue, catecholamines tend to restore the resting potential toward normal. The β-adrenergic blocking properties of propranolol could negate this effect of catecholamines on resting potential and thus cause slowing of conduction in the ischemic zone. Since catecholamines have no effect on resting transmembrane potential when it is normal, no similar effect of β-adrenergic blockade would occur in the normal zone.

The different character of the cellular action potential in ischemic tissue also may modify the effects of propranolol. Slow responses, which are mediated by a slow inward calcium current, may be responsible for impulse propagation in the ischemic zone. Since these currents are enhanced by catecholamines, the β-adrenergic blocking properties of propranolol may selectively depress conduction in the ischemic zone because of a selective effect on slow responses.

Because the present study was performed under anesthesia with pentobarbital, there may have been an influence of this agent on the results. Although direct electrophysiological effects of pentobarbital on Purkinje fibers or ventricular muscle have not been described to date, the agent has vagolytic properties. What influence vagolytic properties may have had in modifying the effects of propranolol in the present study is not clear. Inhibition of vagal tone in itself might have a slight but probably not a great effect on intraventricular electrophysiological parameters.

The observations made in our present study permit certain speculations on which electrophysiological effects of propranolol curtail ventricular arrhythmias due to ischemia. First, it should be noted that ventricular arrhythmias occurring in the first 15 minutes of ischemia probably are reentrant and not automatic since automaticity is not increased at this time. By slowing conduction (Fig. 2) to the point of block and prolonging refractoriness (Fig. 3) in the diseased (ischemic) segment of the reentrant pathway, propranolol may abolish reentrant cycles by creating bidirectional block where previously there was one-way block.

Furthermore, one important mechanism for reentry is a boundary current which is caused by an action potential duration that is shorter in ischemic cardiac tissue than in normal tissue. The potential differences thus created during the latter part of the action potential cause flow of depolarizing current and propagation of reentrant impulses back from the normal to the ischemic zone. Relatively slow conduction in the ischemic zone enhances this mechanism.

The observed effects of propranolol on the electrophysiological interplay between ischemic and normal zones may curtail reentry that is due to boundary currents. First, propranolol considerably reduced the disparity in APD between ischemic and normal zones (Fig. 3). It is of interest that this effect would have been most difficult to predict from studies on individual cardiac cells in isolated tissues. Second, by prolonging refractoriness in the ischemic zone, an effect of relatively great magnitude (Fig. 3), propranolol would curtail propagation of the impulses that are due to boundary currents, because these impulses are transmitted from the normal to the ischemic zone. Further, by reducing the APD/ERP ratio (Fig. 4), propranolol generally increased refractoriness in the latter part of the action potential, when boundary currents arise, and thus made propagation of impulses due to these currents less likely.

The distribution of propranolol in the ischemic zone is an important consideration in relation to interpretation of our present study; unfortunately, few data are available. Propranolol and other drugs might reach the ischemic zone by direct diffusion from the left ventricular cavity or from adjacent normal myocardium or by collateral or other intact blood flow. Because of nonuniform drug distribution, certain parts of the ischemic zone may attain a higher local drug concentration than others. These include the endocardium, where diffusion from the left ventricular cavity could quickly influence conduction via the Purkinje system, and the periphery of the ischemic zone, where drug diffusion from adjacent normal myocardium could influence the formation of boundary currents. Overall, the propranolol concentration probably was lower in the ischemic than in the normal zone during the present study though the more marked electrophysiological actions there still could be consistent with potentiation of its effects. Alternatively, certain or perhaps all of the effects of propranolol may have been mediated indirectly through the nervous system rather than by direct action on the heart.

Finally, in a previous study, we examined the effects of lidocaine during acute myocardial ischemia. Like propranolol, lidocaine reduced the frequency of ventricular beats and it had several electrophysiological properties in common with propranolol. Lidocaine slowed intraventricular conduction only in the ischemic zone, reduced the disparity in APD between ischemic and normal zones, prolonged refractoriness in the ischemic zone, and reduced the APD/ERP ratio in both zones. The significance of these observations may become more apparent when other drugs are examined in the same or similar experimental models.

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**Effects on Myocardial Contractility of Blood-Borne Material Released from the Feline Small Intestine in Simulated Shock**

**OVE LUNDGREN, M.D., PH.D., ULF HAGLUND, M.D., PH.D., OLE ISAKSSON, M.D., PH.D., AND TETSUO ABE, M.D.**

**SUMMARY**

There is a pronounced derangement in cardiovascular function in the cat after a 2- or 3-hour period during which shock is simulated in the small intestine by regional hypotension (BP = 30-35 mm Hg) during activation of vasocostrictor nerve fibers. It has been proposed that these effects are caused by blood-borne cardiodepressant substance(s) released from the "shocked" small intestine. To obtain further evidence for this hypothesis we performed a study on two heart preparations in vitro. Rabbit papillary muscles or isolated beating rat hearts were exposed to intestinal venous plasma obtained from control cats and from cats subjected to simulated intestinal shock for 2 or 3 hours. While control plasma induced only a slight depression of myocardial contractility, plasma from "shocked" intestine caused a significant decrease in peak isometric tension of papillary muscles. Since the experiments on papillary muscle indicated that time to peak tension was largely unaffected by the plasma samples, we conclude that the feline intestine in shock releases material into blood that exerts a negative inotropic effect on the myocardium.

**IN HIS classic work, Traumatic Shock, Cannon** suggested that a toxic factor of bacterial or tissue origin might be of importance in explaining the irreversibility of shock. Since then claims have been made repeatedly that certain sub-

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**From the Departments of Physiology and Surgery II, University of Göteborg, Göteborg, Sweden. Supported by grants from the Swedish Medical Research Council (14X-2855 and B75-4802), from the Clara and Lilly Dahlstrom Fund, and from the Faculty of Medicine, University of Göteborg.**

**Dr. Abe was on leave of absence from the Department of Surgery, Yokohama City University, Yokohama, Japan.**

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