The Effects of Propranolol on Cardiac Conduction

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SUMMARY

The effects of propranolol, 0.1 mg/kg given intravenously, on atrioventricular (A-V) conduction and intraventricular (IV) conduction were studied in eight patients. Atrial pacing was used to control the heart rate. His bundle electrograms were recorded, and the interval from the pacing impulse to the His bundle electrogram (P-H interval) was used as a measure of A-V conduction and the interval from the His bundle electrogram to the S wave (H-S interval) was used as a measure of intraventricular conduction. Propranolol significantly prolonged the P-H interval in every patient at all paced heart rates, and it had no effect on the H-S interval. In two patients propranolol prolonged the effective refractory period of the atrioventricular conducting tissue.

In four dogs during His bundle pacing, propranolol (4 mg/kg iv) had no effect on intraventricular conduction as measured from the His bundle pacing spike to S wave (H-S interval). In two dogs with prolonged H-S intervals secondary to toxic doses of digitalis and procainamide, propranolol had no effect on IV conduction. It is concluded that propranolol prolongs A-V conduction and has no effect on IV conduction when administered to patients in clinically effective dosages. Propranolol's effects on cardiac conduction can be explained on the basis of its capacity to produce beta-adrenergic blockade.

Additional Indexing Words:
Effective refractory period
Intraventricular conduction
Propranolol

PROPRANOLOL has recently been introduced as a useful agent in the treatment of a variety of cardiac arrhythmias.1-6 It slows sinus and atrial tachycardias and can abolish ectopic ventricular rhythms. In addition, propranolol slows the ventricular response in patients with atrial tachycardia, flutter, and fibrillation.

It is unclear whether propranolol's effects on cardiac arrhythmias are due to its capacity to produce beta-adrenergic blockade or to a nonspecific action.7

In this investigation the technic of recording His bundle electrograms8 was used to study the effects of propranolol on cardiac conduction in man. In addition, the effects of propranolol on intraventricular conduction were studied in six dogs during His bundle pacing.8

Methods

Human Studies

Right heart catheterization was performed on eight patients who were in a postabsorptive, nonsedated state. All patients were informed of the nature of the study and a signed consent was obtained. All subjects were in sinus rhythm with a P-R interval of less than 200 msec. Two of the eight patients had multifocal premature ventricular contractions (PVCs). None of the patients had a history of congestive heart failure or...
bronchospasm and none were taking cardiotonic drugs. Under local anesthesia, a tripolar electrode catheter was introduced percutaneously into the right femoral vein and fluoroscopically positioned at the tricuspid valve. The proximal terminals of the electrode catheter were led into the A-C input of an ECG preamplifier to record bipolar electrograms by using a distribution switch box.* His bundle activity was recorded at frequency settings of 40 to 500 cps. A lead II ECG was simultaneously recorded. An additional bipolar electrode catheter was introduced into an antecubital vein and fluoroscopically positioned against the lateral wall of the right atrium. This catheter was used to pace the right atrium up to 140 beats/min. The right atrium was stimulated by a battery-powered pacemaker† (model 5837) which delivered impulses of 2-msec duration. The milliamperage was adjusted (2 × threshold) to assure reliable atrial capture. All electrical equipment was carefully grounded. The interval from the pacing spike to the His bundle electrogram (P-H interval) was used as a measure of atrioventricular (A-V) conduction. The interval from the His bundle to the S wave (H-S interval) was used as a measure of intraventricular conduction. All records were taken on a multichannel oscillographic photographic recorder* at a paper speed of 200 mm/sec. After control records were obtained propranolol 0.1 mg/kg was administered iv over a period of 3 to 4 min. Atrial pacing was then repeated at 5, 10, and 15-min intervals after the administration of the drug.

In two patients the effects of propranolol on the effective refractory period (ERP) of the atrioventricular conducting tissue was measured. The ERP may be defined as the largest interval between two atrial stimuli, both of which cause an atrial depolarization, but the second stimulus fails to evoke a propagated ventricular depolarization. This measurement is obtained by applying premature atrial stimuli (2 × threshold) at varying intervals within the R-R cycle. The premature atrial stimulus was coupled off the preceding QRS complex.

**Dog Studies**

After noting that propranolol had no effect on intraventricular conduction in man, it was decided to administer the drug in higher dosages to dogs. In six open-chested dogs, two Teflon-coated wires were inserted into the His bundle, and His bundle pacing was accomplished at rates of 160 to 240/min. The details of the method have been described previously. The His bundle pacing spike to S wave (H-S interval) was used as a measure of total intraventricular conduction. In four animals propranolol was administered in divided doses to a total iv dose of 4 mg/kg. To study the effects of propranolol on an abnormal conducting system, in two dogs ouabain was infused at a rate of 0.25 μg/kg/min until the onset of a stable ventricular tachycardia. In both dogs procainamide, 30 mg/kg iv, failed to convert the arrhythmia to normal sinus rhythm. Subsequent administration of propranolol in a dose of 3 or 4 mg/kg iv converted both arrhythmias. Measurements of total intraventricular conduction were made during His bundle pacing before and after the administration of each drug.

### Table 1

**Effects of Propranolol on the P-H Interval (msec) in Man**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Paced rate 100/min</th>
<th>Paced rate 120/min</th>
<th>Paced rate 140/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>Pr</td>
<td>Δ</td>
</tr>
<tr>
<td>B.L.</td>
<td>145</td>
<td>160</td>
<td>+15</td>
</tr>
<tr>
<td>K.M.</td>
<td>200</td>
<td>214</td>
<td>+14</td>
</tr>
<tr>
<td>H.B.</td>
<td>130</td>
<td>145</td>
<td>+15</td>
</tr>
<tr>
<td>A.Y.</td>
<td>205</td>
<td>235</td>
<td>+30</td>
</tr>
<tr>
<td>A.J.</td>
<td>168</td>
<td>184</td>
<td>+16</td>
</tr>
<tr>
<td>P.C.</td>
<td>185</td>
<td>204</td>
<td>+19</td>
</tr>
<tr>
<td>L.K.</td>
<td>135</td>
<td>145</td>
<td>+20</td>
</tr>
<tr>
<td>N.P.</td>
<td>184</td>
<td>218</td>
<td>+34</td>
</tr>
<tr>
<td>Average</td>
<td>169</td>
<td>188</td>
<td>+20.4</td>
</tr>
<tr>
<td>sp</td>
<td>29.3</td>
<td>34.9</td>
<td>32.2</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Abbreviations: C = control; Pr = propranolol; P = value obtained by t-test for paired samples.
Results

Human Studies

There were no untoward side effects from the intravenous administration of propranolol. The blood pressure remained stable in all patients. The average systolic blood pressure was 4.6 mm Hg lower after injection of the drug.

Propranolol prolonged the P-H interval in every patient at all paced heart rates (table 1). The control values of the P-H intervals in the eight patients at paced heart rates of 100, 120, and 140 beats/min averaged 169, 186, and 202 msec, respectively. After the administration of propranolol the P-H intervals averaged 188, 207, and 230 msec. These changes represent a significant prolongation of the P-H interval at all paced rates. Propranolol did not prolong the H-S interval in any of the eight patients. A representative recording is presented in figure 1. During atrial pacing at a rate of 120/min, the P-H, H-Q, and H-S intervals were 186, 62, and 142 msec. After the administration of propranolol the P-H interval was prolonged to 212 msec, but the H-Q and H-S intervals were unchanged.

Figure 2 illustrates the effects of propranolol on the effective refractory period (ERP) of atroventricular conducting tissue. In the control state (top panel) a premature atrial depolarization (P') is followed by propagated ventricular response. It should be noted that the P-H and H-S intervals of the premature beat are longer than those of the regular sinus beat. Thus conduction was slowed proximal and distal to the His bundle, presumably in the A-V node and in the specialized conducting tissue of the ventricle. The premature impulse was brought in closer to the sinus beat, and at a P-P' interval of 380 msec no propagated ventricular response followed the atrial depolarization (middle panel, fig. 2). The absence of a His deflection following the

![Figure 1](http://circ.ahajournals.org/)

The effect of propranolol, 0.1 mg/kg iv, on the P-H, H-Q, and H-S intervals during atrial pacing at a rate of 120/min. In the control recording the P-H interval was 186 msec. Propranolol prolonged the P-H interval to 212 msec. The H-Q and H-S intervals remained the same (62 and 142 msec, respectively). PI denotes the pacer impulse. P corresponds to the P wave and the atrial electrogram. H denotes the His bundle electrogram. HR = heart rate.
Figure 2

The effects of propranolol on the effective refractory period (ERP) of atrioventricular conducting tissue. In the control state (top panel) at a P-P' interval of 430 msec, the P' is conducted aberrantly, and the P-H and H-Q intervals are prolonged. At a P-P' interval of 380 msec (middle panel), P' is not followed by a propagated ventricular response. Thus the ERP was 380 msec. After administration of propranolol the ERP was 430 msec (lower panel).

P corresponds with the P waves and atrial electrograms of the regular sinus beats. P' corresponds with the P waves and atrial electrograms of the premature impulses. Note that P' is preceded by a pacing spike. H denotes the His bundle electrogram. HR = heart rate.

nonconducted P wave indicates that the block was proximal to the His bundle. Thus the ERP was 380 msec. Following administration of propranolol, the sinus rate fell to 55/min, and the ERP was prolonged to 430 msec as demonstrated in the lowest panel of figure 2, where the premature atrial depolarization (P') is not followed by a propagated ventricular response. In the other patient studied propranolol prolonged the ERP of the atrioventricular conducting tissue from 320 to 360 msec.

In both patients with VPCs propranolol had no effect on the arrhythmia. However, prior to the administration of the drug, the VPCs were suppressed at atrial pacing rates of 120/min in both patients, whereas after administration of propranolol the VPCs were suppressed at an atrial pacing rate of 100/min as illustrated in figure 3. In the top panel multifocal VPCs are evident during atrial pacing at a rate of 100/min. Parenthetically, it should be noted that each VPC is preceded by a P wave. There is an H spike, partially obscured by a time line, associated with the first VPC. However, the upstroke of the aberrant QRS complex occurs prior to the H spike. Therefore, it is unlikely that the aberrant QRS was conducted from above. There is no H spike associated with the second VPC. After propranolol

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(lower panel) there were no VPCs at an atrial rate of 100/min.

**Dog Studies**

Although propranolol was administered to six dogs in a dosage 40 times greater than that used clinically, it had no significant effect on intraventricular conduction. In four dogs the average control H-S interval during His bundle pacing was 71 msec, and after propranolol (4 mg/kg iv) it remained 71 msec. In two dogs with prolonged H-S intervals secondary to toxic doses of ouabain and procainamide, propranolol again had no effect on the H-S interval. A representative experiment is shown in figure 4. This dog had developed ventricular tachycardia due to a toxic dose of ouabain. The arrhythmia was abolished by overdriving the ventricle with His bundle pacing at a rate of 210/min, and the H-S interval as measured from the pacing spike to termination of the QRS complex was 61 msec. Procainamide, 30 mg/kg iv, failed to abolish the ventricular tachycardia, and during His bundle pacing at a rate of 210/min, the H-S interval widened to 77 msec. Subsequent administration of propranolol terminated the arrhythmia, and there was no further prolongation of the H-S interval; it remained 77 msec.

**Discussion**

The present study demonstrates that when propranolol is administered during fixed-rate atrial pacing it prolongs atrioventricular (A-V) conduction without affecting intraventricular conduction. However, when the drug is used clinically, its ability to slow the sinus rate indirectly enhances A-V conduction, since A-V conduction time is shorter at a slower heart rate. These two effects of the drug may counteract one another as illustrated in figure 2. In the upper two panels at a sinus rate of 67/min the P-H interval was 105 msec. After the administration of propranolol the sinus rate fell to 55/min, but the P-H interval remained 105 msec. Similarly, Stern and Eisenberg reported that propranolol prolonged the P-R interval in only 12 of 21 patients. In contrast in this study during fixed-rate atrial pacing propranolol prolonged A-V conduction in all patients.

It has been shown in the experimental animal that stellate stimulation or the
administration of catecholamines\textsuperscript{14} shortens A-V conduction. Using the technic of recording His bundle electrograms in man, we have noted that isoproterenol shortens the P-H interval but has no effect on the H-S interval.\textsuperscript{11} Thus propranolol's prolongation of the P-H interval and lack of effect on the H-S interval can be explained on the basis of its capacity to produce beta-adrenergic blockade. It has been suggested, however, that propranolol's antiarrhythmic effect is not related to its capacity to produce beta-adrenergic blockade but rather to a nonspecific effect. Davis and Temte\textsuperscript{15} recently presented further evidence for this view and discussed the relevant work of others. The dose required to terminate experimentally induced arrhythmias in dogs\textsuperscript{16} and cats,\textsuperscript{17} however, is 60 to 100 times greater than the clinically effective dosage and far exceeds the dose required for beta-adrenergic blockade. This dichotomy suggests that the mode of action of the drug in man may be different from that in the experimental animal. Alternatively, catecholamines may be more important in the genesis of arrhythmias in man than in the genesis of similar arrhythmias in the experimental animal.

Conduction velocity is related to the rate of rise of the cardiac action potential (the dv/dt of phase 0).\textsuperscript{18} Davis and Temte\textsuperscript{15} found that propranolol depressed the dv/dt of phase 0 of the transmembrane action potential of Purkinje and ventricular muscle fibers of dogs. However, this effect of the drug in contrast to its effects on phases 2 and 3 of the transmembrane action potential only occurred at higher dosage levels in the tissue bath. Therefore, it is of interest in this study that when propranolol was administered in doses 30 to 40 times greater than that used clinically, it had no effect on intraventricular conduction in dogs with normal conducting systems and in dogs with conducting systems stressed by toxic doses of ouabain and procainamide. Previously, Rouse\textsuperscript{19} had reported that propranolol in a dose of 5 mg/kg iv had no effect on the H-S interval in one animal.

Propranolol differs from quinidine and procainamide in that it does not prolong
intraventricular conduction in clinically effective dosages. The ability of quinidine and procainamide to prolong intraventricular conduction is believed to be important in the genesis of spontaneous ventricular arrhythmias which are sometimes seen after the administration of these drugs. It has been suggested that the ability of these drugs to slow intraventricular conduction results in localized unidirectional blocks producing re-entrant arrhythmias. In contrast Davis and Temte have demonstrated in isolated Purkinje fibers that propranolol can abolish decremental conduction. There have been no clinical reports of spontaneous ventricular arrhythmias arising after the administration of propranolol. Despite this advantageous property of propranolol, the drug’s usefulness as an antiarrhythmic agent is impaired by its negative inotropic effects, and when administered intravenously it must be given with caution.

The use of His bundle recordings gives a more accurate analysis of the effective refractory period of atrioventricular conducting tissue than was previously available. Using the technic of Krayer and associates, modified by Linhart, and co-workers, we have noted that the premature atrial impulses can be blocked either proximal or distal to the His bundle. In both patients in this study, the critical premature atrial impulse that defined the effective refractory period was blocked proximal to the His bundle. After the administration of propranolol, the effective refractory period was prolonged, and again the impulse was blocked proximal to the His bundle. This is further evidence that propranolol’s effects on atrioventricular conduction are mediated proximal to the His bundle, presumably in the A-V node.

Recently Wittenberg and Lown have suggested that the slowing of the sinus rate induced by propranolol may enhance rather than depress ventricular arrhythmias. In the two patients in this study with multifocal VPCs, propranolol had no effect on the arrhythmia, although in both patients the VPCs were suppressed at a lower atrial pacing rate after the administration of the drug (fig. 3). Thus propranolol had an antiarrhythmic effect in both patients that was not evident at the slow sinus rate induced by the drug. Increasing the sinus rate by atropine or atrial pacing may enhance the usefulness of propranolol in the treatment of ventricular arrhythmias. The combination of atrial pacing and propranolol has been effective in the control of refractory ventricular arrhythmias.

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References
