The Effect of Digitalis on Refractoriness of the Intact Canine HPS

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SUMMARY The effect of therapeutic doses of digitalis on functional (F), relative (R) and effective (E) refractory periods (RP) of the HPS was studied in 12 open-chested, innervated adult mongrel dogs (10-20 kg) during control and 15, 30 and 45-60 min after 0.016 mg/kg of intravenous ouabain. To determine the stability of the preparation and to assess time-dependent changes in the HPS, another six dogs (Group II) had similar studies, but without drug administration. In all dogs, the His bundle was paced by using the plunge wire technique at a predetermined cycle length (CL) and a premature stimulus (S2) to the His bundle was introduced at decreasing S1, S2, intervals. Following ouabain, in Group I dogs, at the longest CLs tested (45±125 msec; ±sd) there was a significant increase in the FRP (+4.34%; P < 0.05), RRP (S2 S1) (+6.57%, P < 0.05), RRP (Ab) (+6%, P < 0.05) and ERP (+5.2%, P < 0.05) of the HPS. These significant changes were generally observed 30 minutes after drug administration. Changes in RPs were of greater magnitude at longer CLs (>400 msec), but insignificant at shorter CLs (<400 msec). The H-V interval during sinus rhythm and the S1, S2, interval during His bundle pacing at all CLs did not change after ouabain. In Group II dogs there were no significant change in His-Purkinje refractoriness over 60 minutes. These findings suggest that therapeutic doses of digitalis 1) tend to increase refractoriness within the HPS to a very small degree, 2) have no appreciable effect on His-Purkinje conduction, and 3) affect CL-dependent changes in refractoriness. The His bundle extrastimulus method is useful in studying the HPS in the intact heart.

ALTHOUGH THE EFFECT of digitalis glycosides on the atrioventricular (AV) conduction system has been extensively studied, adequate data are not available on its effect on refractoriness of the intact mammalian His-Purkinje system (HPS). Measurements of refractory periods (RPs) within the HPS by the atrial extrastimulus method depend on 1) cycle length (CL) of stimulation, 2) the functional RP of the AV node and 3) the state of His-Purkinje refractoriness itself. Clinical studies are often limited in their assessment of the effects of digitalis on His-Purkinje refractoriness since, during antegrade conduction the functional RP of the AV node frequently exceeds refractoriness of the HPS. Furthermore, the well-established effect of digitalis on the AV node precludes the determination of refractoriness within the HPS. To overcome the above limitations, the effect of therapeutic doses of digitalis on the HPS were assessed by direct stimulation of the bundle of His. Although His bundle stimulation is a well-established technique, no systematic study has used this method to study His-Purkinje refractoriness or to assess the effects of drugs.

Materials and Methods

Studies were performed on 29 adult mongrel dogs (10-20 kg) anesthetized with α-chloralose (100-200 mg/kg). After tracheal cannulation, the dogs were ventilated with room air using a Harvard respirator. A thoracotomy at the level of the fourth intercostal space was performed, and the lateral surface of the right atrium and basal portions of the right ventricle were exposed. The heart was suspended in a pericardial cradle. Twenty-two gauge needles containing two teflon-coated stainless steel wires were plunged into the region of the sinus node, Bachmann's bundle and the coronary sinus for recording local electrograms. A 23 gauge needle containing four teflon-coated stainless steel wires was plunged into the region of the bundle of His for recording from and pacing of the His bundle.

In previous unpublished observations, and in four dogs in this study, the His bundle and bundle branches were dissected with the wires in place. The wires were located in close proximity to the proximal His bundle. In three dogs, the sinus node was crushed in order to pace the bundle of His at long CLs. Bipolar electrograms from the region of the sinus node, Bachmann's bundle, coronary sinus, His bundle with two or more ECG leads and time lines generated at 10, 100 and 1000 msec were simultaneously displayed on a multichannel oscilloscope (Electronics for Medicine Dr 12) and recorded on photographic paper at paper speeds of 150-200 mm/sec.

Stimulation Technique

The His bundle was stimulated with a programmed digital stimulator which delivered rectangular impulses of 1.5 msec duration and 10 V amplitude. The His bundle was stimulated at a predetermined CL (S1, S2) and a premature stimulus (S3) was introduced after every eighth basic drive beat at progressively decreasing (by 10 msec) S1, S2 intervals up to the point at which S2 did not propagate to the ventricle. The
shortest $S_1$ $S_2$ interval at which $S_2$ conducted was then defined and $S_2$ was decreased by 1 msec intervals up to the point of refractoriness.

Consistent His bundle stimulation could be achieved in 18 of 29 dogs. After control determination of refractory periods at one or more CL in 12 of 18 dogs (group I), 0.016 mg/kg of ouabain was administered intravenously and RPs were assessed at 15, 30 and 45–60 minutes after the drug. To determine the stability of such a preparation and to assess any time-dependent changes in His-Purkinje refractoriness, six dogs (group II) had similar studies at control, 15, 30 and 45–60 minutes, but without drug administration. A continuous intravenous infusion of normal saline (100–300 ml/hr) was administered to all dogs. Arterial $P_o$ was 63–128%, pH 7.35–7.55 and serum K was 3–3.9 mEq before administration of ouabain. None of the dogs developed digitalis toxicity, as evidenced by the absence of ventricular or junctional beats, ventricular tachycardia and AV block.

**Definition of Terms**

Conduction intervals:

* $A-H$ interval was measured from the onset of the low atrial electrogram to the onset of the His bundle electrogram.

* $H-V$ interval was taken as representative of His-Purkinje conduction during sinus rhythm. This interval was measured from the onset of the His bundle deflection to the earliest point of ventricular activation on the surface ECG tracing or the local ventricular electrogram.

* $S_1 V_1$ interval represents His-Purkinje conduction during His bundle pacing. This interval was measured from the onset of the stimulus artifact to the earliest point of ventricular activation on the ECG tracing or the local ventricular electrogram.

* $S_2 V_2$ interval represents His-Purkinje conduction during His bundle premature stimulation. This interval was measured from the onset of the premature stimulus artifact to the earliest point of ventricular activation on the ECG tracing or the local ventricular electrogram.

Refractory Periods:

* **Functional Refractory Period (FRP) of the His-Purkinje System (HPS)** was defined as the shortest $V_1$ $V_2$ interval in response to any range of $S_1$ $S_2$ intervals.

* **Relative Refractory Period (RRP) of the HPS** was defined as the longest $S_1$ $S_2$ interval at which $S_2$ conducted to the ventricle with 1) longer $S_2 V_2$ interval than the basic drive beat (RRP-$S_2 V_2$), and/or 2) aberration of the QRS complex (RRP-Abs).

* **Effective Refractory Period (ERP) of the HPS** was defined as the longest $S_1$ $S_2$ interval at which $S_2$ did not propagate to the ventricle. In defining the ERP, the HPS was considered as a single unit because 1) during His bundle stimulation, the His bundle deflection was not separable from the stimulus artifact; 2) in most dogs during premature stimulation, the His bundle did not emerge from the stimulus artifact, and 3) multiple recording sites were absent along the course of the bundle branch Purkinje system. However, it is to be recognized that effective refractoriness by the current technique may be representative of the His bundle and/or of the bundle branch Purkinje system.

In four dogs, at critical $S_1$ $S_2$ intervals, $H_2$ consistently emerged from the stimulus artifact. In these dogs additional RPs could be assessed.

* **RRP of the His bundle** was defined as the longest $S_1$ $S_2$ interval at which $H_2$ emerged from $S_2$.

* **RRP of the Bundle Branch Purkinje System** was defined as the longest $S_1$ $H_2$ or $S_1$ $H_2'$ (in the presence of split His bundle potentials) conducted with an $H_2$ $V_2$ longer than the basic $S_1 V_1$ interval.

* **ERP of the His bundle** was defined as the longest $S_1$ $S_2$ interval at which $S_2$ is not conducted to the ventricle, provided that latency of the bundle of His (emergence of $H_2$ from $S_2$) was identified in the preceding $S_1$ $S_2$ interval.

* **ERP of the Bundle Branch Purkinje System** was defined as the longest $S_1$ $H_2$ or $H_2'$ which was not conducted to the ventricle. Statistical analyses were made, by using the Student $t$ test for paired analysis. Results given are the mean ± standard deviation.

**Results**

**Validation of His Bundle Pacing**

Bundle of His pacing was judged as adequate only when all of the following were present: 1) the $S-V$ interval was within 1–2 msec of the $H-V$ interval of sinus beats, 2) the QRS configuration and duration, as determined by simultaneously recorded leads 1, 2, 3, and $V_1$ were identical to sinus beats, 3) the $S-V$ interval remained isoelectric and 4) the onset and waveform of the $V$ electrogram (on the His bundle electrogram tracing) was unchanged from sinus beats.

In 11 of 18 studies, His bundle pacing was associated with retrograde atrial activation, and in seven of 18 studies His bundle pacing was associated with simultaneous activation of the atria. For both groups I and II dogs the average $S_1 V_1$ interval was $32.38 ± 3.8$ msec and the average $H-V$ interval was $33.3 ± 3.0$ msec. In no experiment did the $S_1 V_1$ interval vary by more than 1 msec from the spontaneous $H-V$ interval. In all studies His bundle pacing was accomplished at an MA of one or less.

**Group I**

**His-Purkinje Conduction**

The average control $H-V$ interval was 31.66 ± 2.4 msec, and there was no detectable change after ouabain (figs. 1 and 2). At all CLs tested, the individual $S_1 V_1$ intervals during His bundle pacing were similar before and after drug administration.

**His-Purkinje Refractory Periods**

Cumulative data for His-Purkinje RPs are shown in table 1. Altogether, 27 CLs (range 250–700 msec) were tested. Statistical significance was determined by using RPs at the longest and shortest CLs.
Figure 1. Control tracings during sinus rhythm and premature stimulation of the His bundle at varying coupling intervals. Tracings in each panel from top to bottom are ECG leads 2 and V1, electrograms from the region of the sinus node (SN), Bachmann's bundle (BB), coronary sinus (CS), His bundle (HBE), stimulus artifact (SA) and time lines (TL) generated at 10, 100 and 1000 msec. Left hand side of panel A shows a sinus beat with an A-H interval of 50 msec and an H-V interval of 30 msec. Right hand side of panel A shows His bundle pacing at a cycle length of 600 msec and a premature His bundle stimulus introduced at an S1, S2 interval of 340 msec. Note that during His bundle pacing, the QRS complex in leads 2 and V1 is similar to that of the sinus beat. Similarly, there is an isoelectric segment between the SA and the onset of the QRS complex and the S1, V1 interval is identical to the H-V interval (30 msec). Note also simultaneous atrial pacing during His bundle stimulation. In panel B at an S1, S2 interval of 320 msec, S2 is conducted with QRS aberration (relative refractory period (RRP)/Ab) and an S1, V2 interval of 35 msec (RRP-S1, V2), longer than the basic S1, V1 interval. Panel C shows a coupling interval of 230 msec, S2 is not conducted to the ventricle (effective refractory period of the His-Purkinje system).
shows data at control, 15, 30 and 45–60 minutes after ouabain in individual dog experiments.

Functional Refractory Periods of the His-Purkinje System

The FRP of the HPS increased by an average of +4.34% after ouabain, which was statistically significant \( P < 0.05 \) at 30 minutes. Six of 12 dogs showed a 10–45 msec increase, four of 12 dogs (nos. 5, 8, 9 and 12) showed either no change or a 5 msec increase, whereas two dogs (nos. 10 and 11) showed a 5–20 msec decrease at one or more CL.

Relative Refractory Period of the His-Purkinje System

During control studies RRP (Ab) preceded RRP \( (S_2 V_2) \) in seven of 12 dogs; in three of 12 dogs RRP

FIGURE 2. Shows tracings post-digitalis in the same dog as in figure 1, studied at a cycle length of 600 msec. Left hand side of panel A shows a sinus beat with an A-H interval of 100 msec and an H-V interval of 30 msec. Right hand side of panel A shows His bundle pacing at a cycle length of 600 msec and premature stimulation at an \( S_1 S_2 \) interval of 390 msec. At an \( S_1 S_2 \) interval of 370 msec (panel B), \( S_2 \) is conducted with QRS aberration (relative refractory period (RRP)/Ab) and \( S_2 V_2 \) prolongation (RRP-\( S_2 V_2 \)). In panel C, at an \( S_1 S_2 \) interval of 300 msec, \( S_2 \) is not conducted to the ventricle (effective refractory period of the His-Purkinje system). Abbreviations: same as for figure 1.
# Table 1. Cumulative Data

<table>
<thead>
<tr>
<th>Group I</th>
<th>Functional Refractory Period</th>
<th>Relative Refractory Period (S&lt;sub&gt;2&lt;/sub&gt; V&lt;sub&gt;2&lt;/sub&gt;)</th>
<th>Relative Refractory Period (Ab)</th>
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<tbody>
<tr>
<td></td>
<td>Control</td>
<td>15 Min</td>
<td>30 Min</td>
</tr>
<tr>
<td>Longest CL</td>
<td>Mean CL = 458 ± 125 (± SD)</td>
<td>230 ± 55</td>
<td>240 ± 64</td>
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<tr>
<td></td>
<td>% Change</td>
<td>+4.34%</td>
<td>+4.34%</td>
</tr>
<tr>
<td>Shortest CL</td>
<td>Mean CL = 354 ± 101 (± SD)</td>
<td>213 ± 48</td>
<td>216 ± 57</td>
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<tr>
<td></td>
<td>% Change</td>
<td>+1.4%</td>
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</table>

(AB) occurred simultaneously with RRP (S<sub>2</sub> V<sub>2</sub>) and in two of 12 dogs RRP (S<sub>2</sub> V<sub>2</sub>) occurred before RRP (Ab) at one or more CL. After ouabain, a similar trend was seen, i.e., in most dogs RRP (Ab) was longer or equal to RRP (S<sub>2</sub> V<sub>2</sub>) values (table 2). After ouabain there was a small but significant increase in both the average RRP (S<sub>2</sub> V<sub>2</sub>) (+6.57%, P < 0.05) and RRP (Ab) (+6%, P < 0.05). Maximum changes in RRP were noted 45–60 minutes after drug administration. In seven of 12 dogs, the increase in RRP (S<sub>2</sub> V<sub>2</sub>) and RRP (Ab) ranged from 10–60 msec, respectively. Figures 1 and 2 illustrate increases in RRP occurring

# Table 2.

<table>
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<tr>
<th>Dog No.</th>
<th>BCL</th>
<th>Functional Refractory Period</th>
<th>Relative Refractory Period (S&lt;sub&gt;2&lt;/sub&gt; V&lt;sub&gt;2&lt;/sub&gt;)</th>
<th>Relative Refractory Period (Ab)</th>
<th>Effective Refractory Period</th>
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<tr>
<td></td>
<td></td>
<td>Control</td>
<td>15 Min</td>
<td>30 Min</td>
<td>45-60 Min</td>
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<td>12</td>
<td>340</td>
<td>175</td>
<td>180</td>
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<td>170</td>
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| Abbreviation: BCL = basic cycle length.
TABLE 1. (Continued)

<table>
<thead>
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<th>Relative Refractory Period</th>
<th>Relative Refractory Period (Ab)</th>
<th>Effective Refractory Period</th>
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<tbody>
<tr>
<td>(S&lt;sub&gt;1&lt;/sub&gt; V&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>(S&lt;sub&gt;1&lt;/sub&gt; V&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>(S&lt;sub&gt;1&lt;/sub&gt; V&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>30 Min</td>
<td>Control 15 Min</td>
<td>Control 15 Min</td>
</tr>
<tr>
<td>45-60 Min</td>
<td>30 Min</td>
<td>45-60 Min</td>
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<td></td>
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<tr>
<td>238 ± 64</td>
<td>243 ± 73</td>
<td>194 ± 48</td>
</tr>
<tr>
<td>+4.38%</td>
<td>+6.57%</td>
<td>+4.12%</td>
</tr>
<tr>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>216 ± 53</td>
<td>216 ± 54</td>
<td>181 ± 42</td>
</tr>
<tr>
<td>+1.8%</td>
<td>+1.8%</td>
<td>+1.1%</td>
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<tr>
<td>NS</td>
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<tr>
<td>222 ± 22</td>
<td>222 ± 19</td>
<td>198 ± 15</td>
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<td>-</td>
<td>-</td>
<td>+0.5%</td>
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<tr>
<td>NS</td>
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</table>

45–60 minutes after ouabain. During control measurements, at an S<sub>1</sub> S<sub>2</sub> interval of 320 msec, S<sub>2</sub> is conducted with bundle branch block aberration and an S<sub>2</sub> V<sub>2</sub> of 35 msec (fig. 1, panel B), the zone of aberration (80 msec) lasted until the ERP of the HPS (230 msec). After digitalis, bundle branch block aberration with S<sub>2</sub> V<sub>2</sub> prolongation occurred at an S<sub>1</sub> S<sub>2</sub> interval of 370 msec (fig. 2, panel B). The zone of aberration decreased to 60 msec and shifted to the right due to earlier occurrence of the ERP of the HPS (fig. 2, panel C).

Effective Refractory Period of the His-Purkinje System

The ERP of the HPS increased in seven of 12 dogs (nos. 1–7) after ouabain. The range of increase was 2–70 msec (figs. 1 and 2, panel C) and the mean increase was 10 msec (+5.2%, P < 0.05). Two dogs (nos. 8 and 9) showed no change in ERP, whereas two dogs (nos. 11 and 12) showed variable effects (i.e., a +10 to –10 msec change from 15 to 45–60 minutes post-ouabain). One dog (no. 10) showed a consistent decrease of 10–30 msec over the entire range of CLs. In this dog a consistent decrease in FRP and ERP also occurred. The latter five dogs were studied at a relatively shorter CL (379 ± 98 msec).

Relative and Effective Refractoriness of the His Bundle

In three dogs from group I, the His bundle deflection (H<sub>2</sub>) emerged from S<sub>2</sub> at critical S<sub>1</sub> S<sub>2</sub> intervals as a single deflection (two dogs) and as split His bundle deflections (one dog). In one of these dogs, digitalis significantly increased the ERP and the ERP of the bundle of 8 His consistently at CLs of both 500 and 400 msec. Figure 3 shows control tracings in this dog (no. 4), studied at a CL of 400 msec. The RRP-Ab and RRP (S<sub>2</sub> V<sub>2</sub>) of the HPS were 220 msec (panel A) and 210 msec, respectively. At coupling intervals of 190–187 msec (panel C), H<sub>2</sub> emerged from S<sub>2</sub> (ERP of the His bundle) and an S<sub>1</sub> H<sub>2</sub> interval of 202 msec was conducted to the ventricle with an H<sub>2</sub> V<sub>2</sub> interval of 35 msec (RRP of the bundle branch Purkinje system). This suggests that the S<sub>2</sub> V<sub>2</sub> prolongation (panel B) before emergence of H<sub>2</sub> probably occurred distal to the His bundle. Furthermore, the RRP of the bundle branch Purkinje system (202 msec) was longer than that of the His bundle (190 msec). At a coupling interval of 186 msec (panel D), S<sub>2</sub> was blocked in the His bundle (ERP of the His bundle). After digitalis (fig. 4) H<sub>2</sub> emerged from S<sub>2</sub> at coupling interval of 240 msec (panel A). Marked latency of 40 and 65 msec is seen at coupling intervals of 220 and 216 msec, respectively (panels B and C). The RRP of the bundle branch Purkinje system was not attained, since corresponding increases in S<sub>1</sub> H<sub>2</sub> intervals of 250 and 280 msec were not associated with H<sub>2</sub> V<sub>2</sub> delays. Furthermore, the QRS complex resulting from an S<sub>1</sub> H<sub>2</sub> interval of 280 msec (panel C) was less aberrant than that seen in panels A and B, suggesting an intra-Hisian gap with partial distal recovery. At a coupling interval of 215 msec (panel D), the His bundle was refractory. Thus, in this experiment both the ERP and the His bundle increased by 50 and 29 msec, respectively. The ERP of the bundle branch Purkinje system could not be attained in either of these dogs, since determination of this RP was limited by His bundle refractoriness.

The Effect of CL of Stimulation on His-Purkinje Refractory Periods

During control measurements there was a significant correlation between CL of stimulation and the FRP (r = 0.826), RRP (S<sub>2</sub> V<sub>2</sub>) (r = 0.839), RRP (Ab) (r = 0.756) and ERP (r = 0.766) of the HPS. Following ouabain the correlation between CL and refractoriness was similar to control. However, the magnitude of increase in RPs were significantly greater at CLs > 400 msec, while at CLs < 400 msec, the changes were insignificant (table 1).
Figure 3. Tracings showing relative and effective refractoriness of the His bundle during the control period. Abbreviations are the same as figure 1. In this dog the sinus node was crushed and the basic rhythm was junctional with retrograde atrial activation. In panel A, the His bundle is being paced at a cycle length of 400 msec. There is 1:1 retrograde atrial activation as seen by the retrograde sequence of the CS, BB and SN electrogram. In panel A, at a coupling interval of 220 msec S₂ is conducted with QRS aberration (RRP-Ab) without S₂ V₂ prolongation. In panel B at a coupling interval of 200 msec, S₂ is conducted with greater degree of aberration and S₂ V₂ prolongation (RRP S₂ V₂). Note that the junctional escape beat (extreme right) has the same configuration and H-V interval as that of the His paced beats. In panel C, at a coupling interval of 187 msec, H₂ emerges from S₂ (RRP of the His bundle) and an S₁ H₂ of 202 msec is conducted with an H₂ V₂ of 35 msec (RRP bundle branch Purkinje system). In panel D, at a coupling interval of 186 msec, S₂ is blocked in the bundle of His.

Figure 5 illustrates the effect of the CL on the ERP of the HPS in dog no. 2, in whom four CLs were tested. During control studies, there was a 10% decrease in the ERP for each 100 msec decrease in CL (from 600 to 400 msec), whereas there was a 20% decrease in ERP when the CL was decreased from 400 to 300 msec. Fifteen minutes after ouabain, a 9% increase in ERP occurred at CLs of 600 and 500 msec and at 45 minutes a 30% and 20% increase occurred, respectively. At CLs of 400 and 300 msec an increase in ERP of 10% and 5%, respectively, occurred only at 30 and 45 minutes after digitalis.
**FIGURE 4.** Tracings in the same dog after digoxin. In panel A, the His bundle is being paced at a basic cycle length of 400 msec. The S1 V1 interval is 30 msec. Note that post-digoxin (D) retrograde atrial activation is markedly delayed, with a 2:1 response during His bundle pacing. Abbreviations: same as for figure 1.

**His-Purkinje Response to Premature Stimulation of the Bundle of His and its Modification by Digitalis**

For each dog and at each CL studied, the intervals between the basic and premature response V1 V2 and S2 V2 were plotted against the corresponding S1 S2 intervals. The V1 V2 interval decreased in proportion to the S1 S2 interval until critical S1 S2 interval was attained when V1 V2 interval reached a minimal value. The V1 V2 curve then plateaued until the ERP of the HPS was reached. The corresponding S1 V2 intervals were constant till the RRP of the HPS, when an increase in S2 V2 interval occurred (fig. 6). Since V1 V2 curve is a function of S2 V2 intervals, variation in V1 V2 curves also depended on the degree of S2 V2 prolongation in the zone of relative refractoriness. The V1 V2 responses observed in this study during premature His bundle stimulation have been previously described by other investigators in the canine and in man during premature atrial stimulation. However, the type III response curve observed in the chronic dog experiments of Hoffman et al.15 and in man by Wit et al.16 and attributed to His-Purkinje delay, were not observed in this study. After digitalis, the V1 V2 curve plateaued earlier in seven of 12 dogs and often increased at critical S1 S2 intervals (in the zone of relative refractoriness) till the ERP of the HPS was reached (fig. 6). The upward shift of the V1 V2 curve was related to greater degree of S2 V2 delay at similar S1 S2 intervals.

**Time-dependent Changes in HPS Refractory Periods (Group II)**

Table I shows cumulative data on changes in refrac-
FIGURE 5. Shows the effect of basic cycle length (BCL) on the effective refractory period (ERP) of the His-Purkinje system (HPS) during control period and 15 and 45 minutes post-digitalis (D) in the same dog (no. 2) studied at four cycle lengths (600-300 msec). Abscissa = BCL in msec. Ordinate — ERP of the HPS. As the BCL is decreased from 600 to 300 msec, there is a decrease in the ERP of the HPS. Fifteen minutes post-D there is a 20 msec increase in ERP from 230 and 220 msec to 250 and 240 msec at BCLs of 600 and 500 msec, respectively, whereas there is no change at BCL of 400 and 300 msec. Forty-five minutes post-D, the increase in ERP is 70 and 60 msec at BCL of 600 and 500 msec, respectively, and 20 and 10 msec at BCL of 400 and 300 msec.

Discussion

Previous studies in the intact canine heart have shown that low or therapeutic concentrations of digitalis 1) slow AV nodal conduction, 1,17-19 2) increase refractoriness of the AV node, 3) decrease ventricular muscle refractoriness 18 and 4) have variable effects on conduction within ventricular muscle and the HPS. 20-22 Digitalis is not known to directly alter the duration of the QRS complex in man, although the chronotropic effects of the drug may unmask rate-related changes. Moreover, by prolonging AV nodal conduction and refractoriness, digitalis reduces or altogether eliminates ventricular aberration resulting from premature atrial impulses, or during atrial fibrillation.

The results of our study suggest that low or therapeutic concentrations of digitalis may 1) increase refractoriness within the HPS to a very small degree, 2) have no appreciable effect on His-Purkinje conduction and 3) affect CL dependent changes in refractoriness. The results also indicate that these are not time-dependent changes. The percentage change in refractoriness seen in this study is in accordance with the microelectrode studies of Rosen et al. 23 who showed a 4.4% increase in duration of the action potential in the absence of ouabain toxicity. However, they did not assess refractoriness in the isolated Purkinje fibers.

The observation that the increase in His-Purkinje RPs was small or insignificant at short CLs, and greater at relatively long CLs in individual dog experiments, may be related to opposing effects of CL on stimulation 24-26 and low concentration of ouabain 27 on membrane resistance. The variable effects seen in three of 12 dogs studied at relatively short CLs may also be related to the latter. Kasebaum 28 and Lee et al. 29 reported that digitalis induces prolongation of the action potential duration and plateau in Purkinje fibers at CLs of approximately 2000 msec. These changes were attributed to a decrease in potassium conductance. 28 Rosen et al. 23 showed similar changes in action potential duration at CLs of 500 msec. Our findings suggest that digitalis tends to increase His-Purkinje RPs at relatively longer CLs (> 400 msec), whereas insignificant or no change occurs at shorter CLs (< 400 msec).

The change in His-Purkinje RPs seen in this study may be related to:

1) direct effect of the glycoside on the HPS. It is possible that the degree of traumatization to the bundle of His during plunging in the individual dog experiment played a role in determining the effect of the drug. However, trauma to the HPS probably did not play a major role, since none of the dogs developed intra-Hisian and/or bundle branch block during or subsequent to plunging. Furthermore, the S1, V1 intervals were similar during pacing at all tested CLs.

2) increased efferent vagal stimulation with withdrawal of sympathetic tone. 30-32

3) direct vagal effects. The third possibility is probably less likely, since there is no strong evidence for parasympathetic innervation of the HPS. Varghese et al. 33 found no effect on His-Purkinje antegrade and retrograde conduction after vagal stimulation and acetylcholine infusion. Moreover, other investigators 34-37 have found no effect of change in vagal tone on His-Purkinje refractoriness while sympathetic nerve stimulation and administration of isoproterenol have been shown to decrease HPS refractoriness.

The design of this study did not allow direct examination of the site of effect of digitalis within the HPS, since in the absence of multiple recording sites and the inseparability of the His bundle deflection...
from the stimulus artifact, the HPS was considered as a single unit. However, findings in the present study suggest that the area of relative refractoriness within the HPS is defined at sites distal to the His bundle, since 1) the RRP of the His bundle was not attained in most experiments both during control and after digitalis, and 2) varying degrees of QRS aberration were seen before attainment of ERP of the HPS. Thus, the observed effects of digitalis on the RRP of the HPS probably occurred at sites distal to the His bundle, namely, the bundle branches, and/or the peripheral Purkinje muscle junctions. In only one of these dogs, delay in excitability of the His bundle was observed after digitalis, as evidenced by an increase in the RRP of the His bundle. The changes in the ERP of the HPS probably occurred within the His bundle and/or the bundle branch Purkinje system.

**Implications**

1) It is unlikely that therapeutic concentrations of digitalis will influence refractoriness within the HPS in man since, A) the effects of the glycoside on the HPS may be offset by delayed conduction and refractoriness of the AV node and B) the effects of digitalis demonstrated in this study were generally observed in the latter part of the V1 V2 response curve (i.e., at shorter coupling intervals before the ERP of the HPS.

2) From the observations made in this study, it is tempting to speculate that closely coupled junctional or His bundle extrasystoles in the presence of digitalis may be conducted with aberration (simulating ventricular premature contractions) or may be blocked in the HPS. Selective digitalis effects on right vs left bundle branches in terms of the type of ventricular aberration was not observed in this study.

3) The model utilized in this study is useful in determining His-Purkinje RPs and the effect of drugs on the HPS.

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Circulation. 1978;58:284-294
doi: 10.1161/01.CIR.58.2.284
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://circ.ahajournals.org/content/58/2/284

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