Effect of Digoxin on Atrioventricular Conduction
Studies in Patients with and without Cardiac Autonomic Innervation

By D. J. Goodman, M.D., R. M. Rossen, M.D., D. S. Cannom, M.D., A. K. Rider, M.D., and D. C. Harrison, M.D.

SUMMARY
The effect of digoxin on atrioventricular (A-V) conduction was compared in five patients with an intact cardiac autonomic nervous system (Group I) and seven patients who had undergone cardiac transplantation (Group II), in whom we have previously shown the transplanted heart to be completely denervated. Small decreases in the atrial effective refractory period (ERP) (from 262 ± 12 to 254 ± 11 msec) and atrial functional refractory period (FRP) (from 304 ± 12 msec to 298 ± 12 msec) were observed in Group I patients after digoxin, but these changes were not significant. However, significant increases in the A-V nodal ERP (from 315 ± 18 msec to 351 ± 17 msec, P < 0.05), and A-V nodal FRP (from 426 ± 42 to 460 ± 46 msec, P < 0.01) were produced by digoxin and were unrelated to changes in cycle length.

In Group II patients with denervated hearts, changes in atrial ERP (from 246 ± 4 to 243 ± 6 during spontaneous sinus rhythm; from 204 ± 10 to 216 ± 8 msec during atrial pacing) and atrial FRP (from 311 ± 12 to 316 ± 11 msec during spontaneous sinus rhythm; from 254 ± 12 to 260 ± 10 msec during atrial pacing) were not significant. However, in contrast to the Group I patients, the digoxin-induced changes in A-V nodal ERP (from 280 ± 22 to 297 ± 18 msec during atrial pacing) and FRP (from 368 ± 18 to 377 ± 18 msec during spontaneous sinus rhythm; from 334 ± 13 to 346 ± 16 msec during atrial pacing) were also statistically insignificant.

Our results demonstrate that the electrophysiologic effects of digoxin on atrioventricular conduction in man are most marked in the atrioventricular node and are dependent on cardiac innervation.

Additional Indexing Words:
Atrioventricular conduction
Autonomic nervous system

THE MECHANISMS by which digitalis affects atrioventricular (A-V) conduction have been a matter of continuing controversy. At least three contributing factors have been proposed including changes in vagal tone, alterations of the sympathetic nervous system, and direct effects of the glycoside.1,6 Studies in man have usually been limited to persons with known heart disease in whom an intact autonomic nervous system is present, or to those patients in whom drug-induced blockade of components of the autonomic nervous system has been effected.4,6,8 Such studies make it difficult to separate the direct electrophysiologic effects of glycosides from those mediated via the autonomic nervous system. Cardiac transplantation has provided us with a unique opportunity to study the functionally normal human heart in the denervated state.9,10 The purpose of this study was to assess the effect of digitalis on A-V conduction in such patients.

Methods
A group of five patients, ranging in age from 34 to 68 years, with various types of cardiac disease and intact cardiac reflexes underwent electrophysiologic study (Group I) (table 1). Four were classified as NYHA Class I, while one patient with a cardiomyopathy was NYHA Class II. Informed consent for the study was obtained from each patient. Cardioactive medications were withheld 72 hours prior to study. At the time of routine yearly evaluation in seven patients, ranging in age from 27 to 55 years, who had undergone cardiac transplantation similar electrophysiologic studies were performed (Group II) (table 1). All were NYHA Class I for cardiac symptoms, receiving immunsup-
Table 1

Clinical, Electrocardiographic and Control Conduction Data for Group I and Group II Patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cardiac diagnosis</th>
<th>Heart rate (beats/min)</th>
<th>QRS duration (sec)</th>
<th>P-A (msec)</th>
<th>A-H (msec)</th>
<th>H-V (msec)</th>
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<td>MV prolapse</td>
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<td>54</td>
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<td>1 year post-transplant</td>
<td>128</td>
<td>0.09</td>
<td>40</td>
<td>80</td>
<td>45</td>
</tr>
</tbody>
</table>

Abbreviations: P-A = interval between the beginning of the P wave and the atrial electrogram recorded by the His bundle catheter; A-H = interval between the atrial electrogram and His bundle electrogram; H-V = interval between the His bundle electrogram and initiation of ventricular depolarization; MV prolapse = mitral valve prolapse; PSVT = paroxysmal supraventricular tachycardia; CM = cardiomyopathy; * = right bundle branch block.

Pressor therapy of corticosteroids and azathioprine. Their weights ranged from 78.6 to 86.4 kg and their serum creatines ranged from 0.8 to 1.2 mg%. The transplanted heart, both at the time of surgery and in subsequent follow-up studies, has been shown to be normal except for its denervated state. The resting ECG and baseline intracardiac conduction intervals were within normal limits except for patient 3 in Group I who had a prolonged H-V interval and patient 1 in Group II who had a right bundle branch block. The data are summarized in table 1.

Studies were performed in the nonedated, postabsorbptive, resting state in the cardiac catheterization laboratory. A tripolar His bundle recording catheter was positioned across the tricuspid valve for recording of the His potential. A quadripolar stimulating-recording catheter was positioned in the high right atrium near the sinus node. The distal electrode pair was used for atrial pacing while the proximal pair recorded a right atrial electrogram. The atrial and His bundle electrograms were displayed along with two surface electrocardiographic traces on a multichannel oscilloscopic recorder (Electronics for Medicine DR-16) and recordings made at paper speeds of 100 and 200 mm/sec. Atrial stimulation was performed utilizing a programmable stimulator (manufactured by M. Bloom, Philadelphia), using stimuli of 2 msec duration and approximately twice diastolic threshold.

Refractory periods were determined using the extra stimulus technique. Beginning late in the cardiac cycle, a premature atrial stimulus (S2) was introduced after every eighth spontaneous sinus beat (Group I and Group II) or driven atrial beat (S1) (Group II only). The prematurity of the S2 was decreased in 20 msec steps until the atrial refractory period was encountered, so that the entire atrial cycle was scanned. After control measurements were obtained, digoxin 1.25 mg i.v. was given over a five-minute period, and the experimental procedure repeated 45 minutes to one hour later. At the termination of the study, amyl nitrite and atropine were administered to Group II patients for evaluation of autonomic innervation, and blood was drawn for determination of the digoxin level 60 to 90 min after its administration. Serum digoxin level in all patients was greater than 5 ng/ml as expected after its acute administration.

Measurements of intracardiac conduction intervals and refractory periods were accomplished according to standard techniques. A1, A2, H1, and V1 are the atrial, His, and ventricular electrograms resulting from either spontaneous sinus beats or driven atrial beats (S1). A2, H2, and V2 represent the atrial, His, and ventricular electrograms resulting from a premature atrial stimulus (S2).

The refractory periods for the A-V conduction system were defined as:

- Atrial effective refractory period (atrial ERP) = longest S1
- S2 interval not resulting in atrial capture by S2.
- Atrial functional refractory period (atrial FRP) = shortest A1-A2 interval achievable.
- A-V nodal effective refractory period (A-V nodal ERP) = longest A1-A2 interval in which A2 does not conduct to the His bundle.

All determinations could not be obtained in all patients.
EFFECT OF DIGOXIN ON A-V CONDUCTION

Table 2

The Effect of Digoxin on Refractory Periods in Group I Patients During Spontaneous Sinus Rhythm*

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Atrium</th>
<th>A-V Node</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERP</td>
<td>FRP</td>
</tr>
<tr>
<td>C Dig</td>
<td>C Dig</td>
<td>C Dig</td>
</tr>
<tr>
<td>1 860 880</td>
<td>280 270</td>
<td>320 320</td>
</tr>
<tr>
<td>2 650 720</td>
<td>250 260</td>
<td>300 290</td>
</tr>
<tr>
<td>3 750 800</td>
<td>240 240</td>
<td>280 280</td>
</tr>
<tr>
<td>4 860 870</td>
<td>240 220</td>
<td>280 270</td>
</tr>
<tr>
<td>5 880 870</td>
<td>300 280</td>
<td>340 330</td>
</tr>
</tbody>
</table>

Mean = 788 828; SEM (SD) = 12 11; P NS NS NS <0.05† <0.01

*All values expressed in msec.
†A-V nodal ERP in control state in patient 5 assumed to be equal to the atrial FRP.
‡Patient 3 not included in statistical analysis.

Abbreviations: CL = cycle length; ERP = effective refractory period; FRP = functional refractory period; C = control; dig = digoxin; NS = not significant.

Results

Tables 2, 3, and 4 summarize the results of electrophysiologic studies in Group I and II patients before and after digoxin.

In the group of five patients with intact cardiac reflexes (Group I), studies were performed during spontaneous sinus rhythm only. Control atrial refractory period values were within the normal range for our laboratory. Digoxin caused an insignificant decrease in the atrial ERP and FRP (table 2).

The A-V nodal ERP could not be measured in patients in whom the atrial FRP was longer than the A-V nodal ERP, since in these cases the still refractory atrium limits A-V conduction. The A-V nodal ERP could be determined in three of five patients before digoxin, and in four of five after the drug. Control A-V nodal refractory periods were normal for our laboratory. The increase in A-V nodal ERP from 315 ± 18 to 351 ± 18 msec in four patients was statistically significant (assuming that before digoxin administration the A-V nodal ERP was equal to the atrial FRP in patient 5) (P < 0.05) (table 2). The true A-V nodal ERP could only be less than the assumed value and hence would tend to minimize any change produced by digoxin in patient 5. The A-V nodal FRP could be determined in all five patients and increased uniformly from 426 ± 42 to 460 ± 46 msec (P < 0.01). It should be noted that the cycle length

Table 3

The Effect of Digoxin on Refractory Periods in Group II Patients During Spontaneous Sinus Rhythm*

<table>
<thead>
<tr>
<th>Patient number</th>
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<tr>
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<tr>
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<td>330 330</td>
</tr>
<tr>
<td>7 470 470</td>
<td>230 260</td>
<td>270 300</td>
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</table>

Mean = 564 564; SEM (SD) = 32 36; P NS NS NS NS

*All values expressed in msec.
†Mean for patients 2, 6, and 7.
‡Mean for patients 1, 2, 4, 6 and 7.

Abbreviations: CL = cycle length; ERP = effective refractory period; FRP = functional refractory period; C = control; dig = digoxin; NS = not significant.
change due to digitalis was insignificant. Figure 1 illustrates the effect of digoxin, 1.25 mg i.v., on the ERP and FRP of the A-V node in patient 1 from Group I. Note the increase in A-V nodal ERP and FRP after digitalis.

In the seven transplant patients (Group II), atrial effective and functional refractory periods were determined both during spontaneous sinus rhythm and during atrial pacing. Neither during sinus rhythm nor atrial pacing did digoxin have a significant effect on the atrial ERP. The atrial FRP measured during both sinus rhythm and atrial pacing did not change significantly (tables 3, 4). In the denervated transplant patients, studies during regular sinus rhythm allowed the determination of the A-V nodal ERP in only three patients due to the limitations of the atrial FRP. However, in these three patients the mean A-V nodal ERP of 340 msec was unchanged by digitalis administration (table 3). During atrial pacing the A-V nodal ERP could be determined in four of seven patients before, and six of seven patients after digoxin administration, increasing in four of six. However, if we assume that the A-V nodal ERP was equal to the atrial FRP in patients 3 and 5 before digoxin, the change in A-V nodal ERP from 280 ± 22 to 297 ± 18 msec did not reach statistical significance (table 4).

The A-V nodal FRP was determined before and after digoxin in five Group II patients during spontaneous sinus rhythm. The increase noted after digoxin was not significant (table 3). During atrial pacing the A-V nodal FRP could be determined on all but one occasion. Assuming the value after digoxin in

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**Table 4**

The Effect of Digoxin on Refractory Periods in Group II Patients During Atrial Pacing*

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<th>FRP C</th>
<th>Dig C</th>
<th>ERP A-V Node C</th>
<th>Dig C</th>
<th>FRP C</th>
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</table>

*All values expressed in msec.
†Mean for patients 2, 3, 4, 5 and 6; A-V node ERP in control state in patient 3 & 5 assumed to be equal to the atrial FRP.
‡Assuming the FRP after digoxin in patient 1 is the shortest H1 − H2 interval obtained.

Abbreviations: CL = cycle length; ERP = effective refractory period; FRP = functional refractory period; C = control; dig = digoxin; NS = not significant.

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**Figure 1**

Effect of digoxin, 1.25 mg i.e., on the A-V nodal refractory periods on patient 1 of Group I with an intact autonomic nervous system. CL = cycle length; A1−A2 = interval between the last spontaneous atrial beat and the premature atrial stimulus; H1−H2 = interval between the last spontaneous His bundle deflection and the His bundle deflection resulting from the premature stimulus. Series of closed, connected circles = control refractory period determination; series of open connected circles = digoxin refractory period determination. The A-V node effective and functional refractory periods are increased after digoxin.

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patient 1 was equal to the shortest $H_1-H_2$ recorded (300 msec), the increase in A-V nodal FRP was also not significant (table 4). It should be noted that resting cycle length did not change in any patient after digoxin administration. Figure 2 illustrates the effect of digoxin, 1.25 mg i.v., on the A-V nodal ERP and FRP during spontaneous rhythm in denervated patient number 7. Note that there is no significant change in A-V nodal ERP or FRP after digoxin.

After the administration of amyl nitrite to the transplant patients, only a small (<5%) increase in donor heart rate was produced. Atropine, 1.5 mg i.v., produced no change in donor heart rate. These results confirm the autonomic denervation in these patients.

**Discussion**

Digitalis preparations have been shown to affect atrioventricular conduction both in animals and man. In the innervated (intact) human heart, ouabain has been shown to increase the P-R interval during atrial pacing when compared to control measurements, but after atropine this effect was abolished. Digoxin has been shown to increase both the effective and functional refractory period of the A-V node in the innervated human heart. In the dog, Mendez and Mendez demonstrated an increase in A-V nodal refractory periods after digitalis, and in the acutely denervated preparation found similar results. Schaal et al. have shown that in the chronically denervated dog heart the functional refractory period of the A-V node is identical before and after digoxin. The findings of Morrow et al. in dogs suggested antiadrenergic, vagomimetic, and direct effects of ouabain.

The transplanted human heart offers us a unique opportunity to study the electrophysiologic effects of cardioactive drugs. The heart is normal anatomically and functionally, as demonstrated at the time of surgery and at routine yearly examinations, except that it lacks neural innervation. Thus, it offers an ideal situation for distinguishing direct drug effects from those mediated by stimulation of the autonomic nervous system either directly or secondary to reflex adjustments. Circulating catecholamines may also directly affect A-V conduction. However, changes in the catecholamine environment did not seem to take place during the studies in transplant patients as judged by a constant heart rate during the entire procedure (table 1).

In both the Group I and Group II patients, digoxin administration had no statistically significant effect on the atrial effective or functional refractory period. The small, insignificant increase in both parameters in Group I patients may have been related to the similarly insignificant increase in cycle length after digoxin. Denes et al. have shown that increases in cycle length are accompanied by an increase in atrial effective and functional refractory period. Alternately, it is possible that because of the postulated opposing autonomic and direct effect of digoxin in the atrium, with the autonomic effect usually predominant, this small change is to be expected. However, only with a larger test group could statistical significance be reached. In Group II patients, in whom the direct effect unopposed by autonomic factors should be more obvious, no significant change in atrial refractory periods could be demonstrated.

In contrast to the minimal electrophysiologic effect in the atrium, digoxin produced significant increases in the A-V nodal effective and functional refractory periods in Group I patients. This may be the result of the influence of digoxin on the autonomic system (vagotonus and sympatholysis) with ultimately a direct effect on the A-V node. In evaluating these drug effects in patients with an innervated, diseased heart it should be remembered that both the underlying

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**Figure 2**

Effect of digoxin, 1.25 mg i.v., on the A-V nodal refractory periods on patient 7 of Group II with cardiac denervation. CL = cycle length; $A_1-A_2$ = interval between the last spontaneous atrial beat and the premature atrial stimulus; $H_1-H_2$ = interval between the last spontaneous His bundle electrogram and the His bundle electrogram of the premature stimulus. Series of closed connected circles = control refractory period determination; series of open connected circles = digoxin refractory period determination. There is no change in A-V nodal refractory periods after digoxin.
autonomic tone and the magnitude of the reflex changes are probably abnormal, and these factors are probably of prime importance in determining the patient’s response to digitalis glycosides.16-18

In contrast to the group of five patients with intact cardiac reflexes, no significant effect of digoxin could be demonstrated on A-V nodal refractory periods in the seven patients with transplanted, denervated hearts. Determination of the A-V nodal ERP during the patient’s spontaneous sinus rhythm could be made in only three patients before and after digoxin, so that statistical analysis was not performed on the data. However, it is possible that the small, insignificant increases in the A-V nodal ERP found during pacing, and the A-V nodal FRP determined during both sinus rhythm and pacing, represent small direct effects of the drug. Again, a larger study group might show the direct effects of digoxin to be important.

In summary, this study has documented the contrasting effect of an acutely administered cardiac glycoside, digoxin, on A-V nodal conduction in patients with a transplanted, denervated human heart when compared to patients with intact cardiac reflexes. In the intact heart, digoxin has been shown to prolong the A-V nodal ERP and FRP irrespective of changes in the cycle length, while in the transplanted heart no statistically significant effects could be demonstrated after acute administration. It is of note that while the study was conducted 45 minutes to 1 hour after the administration of digoxin, so that autonomic effects would be expected to have occurred within the period of observation, later direct effects on the A-V node cannot be excluded. In addition, the patients had been taking no glycosides prior to study and had received an acute bolus of digoxin. It may be that study after chronic administration of the drug would reveal direct electrophysiologic effects on A-V nodal conduction.

These results are applicable to patients with heart disease, especially those with congestive failure. In patients with heart disease, parasympathetic responsiveness is reduced.16 Congestive heart failure both in the experimental animal and in man impairs the cardiac responsiveness to sympathetic stimulation.17, 18 This reduction in autonomic responsiveness finds its ultimate expression in the transplanted heart.8, 10 It would be expected, therefore, that the effect of digitalis on atrioventricular conduction by way of its primary autonomic actions would be blunted in patients with heart disease, especially those with congestive failure. This may help to explain situations in which the amount of slowing of the ventricular response to atrial fibrillation after digitalis administration in patients with congestive heart failure is unexpectedly small.

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