Depressant Effect of Digoxin on Atrioventricular Conduction in Man

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SUMMARY We examined the effect of chronically administered digoxin on atrioventricular (A-V) conduction in nine cardiac transplant recipients. We assessed A-V conduction by measuring the duration from the pacing stimulus to the onset of the QRS complex (S'R interval) and by determining the occurrence of Wenckebach periodicity during rapid atrial pacing. We made measurements during a control period and during a period of digoxin administration of up to 37 days. During the digoxin period, the cycle length at which Wenckebach block occurred was prolonged by 14% of the control value and the S'R interval was significantly prolonged at paced rates of 110 beats per minute and faster. After digoxin was discontinued, the Wenckebach periodicity and S'R interval returned to control values. Atropine and propranolol did not alter digoxin's effect on A-V conduction. We conclude that digoxin exerts a direct (or non-neurally mediated) depressant effect upon A-V conduction in man, although the stress of tachycardia is necessary to demonstrate the effect.

BECAUSE DIGITALIS has both clinical utility and serious toxicity which are dependent upon alterations of A-V conduction, knowledge of its various effects on A-V conduction in man is important. Most studies examining the mechanism whereby digitalis increases A-V nodal refractoriness and slows A-V conduction have emphasized its vagomimetic and antiadrenergic effects.1-4 The existence and magnitude of a direct (or non-neural) depressant effect upon A-V conduction remains controversial. In isolated heart preparations and anesthetized animals, a minor direct effect exists at high concentrations of digitalis.5-9 In man and in intact conscious animals, most studies of A-V conduction in the presence of vagal blockade10-12 or cardiac denervation13-15 have failed to demonstrate that acute intravenous administration of digitalis prolongs A-V conduction, although one report limited to three patients showed that a small effect persisted after atropine administration.15

Therefore, to further explore the mechanism of action of digitalis upon A-V conduction, we examined the effects of digoxin administered chronically to cardiac allograft recipients whose hearts are anatomically denervated. The results indicate that at therapeutic steady-state serum concentrations, digoxin acts directly to slow A-V conduction, but that this effect becomes manifest only when A-V conduction is stressed by tachycardia.

Methods

We performed studies in 12 recipients 2-10 weeks after cardiac transplantation. The investigations were initiated following the acute phase of convalescence after operation and at least one week after the disappearance of measurable serum digoxin concentrations known to persist for several days after cardiac transplantation in patients receiving digoxin prior to cardiac replacement (unpublished data, E.B. Stinson). Serial studies in three patients were interrupted by episodes of cardiac rejection or infection and these patients are excluded from the analysis; the remaining nine patients were free of such complications throughout the study interval. The absence of rejection was confirmed by normal right ventricular endomyocardial biopsies performed before and after each study period. Routine medications included azathioprine, prednisone, sodium warfarin, furosemide, and potassium chloride, but no cardioactive drugs. As a feature of routine management, each patient had two temporary wire electrodes sutured to the donor high right atrium and exteriorized through the anterior chest wall at the time of surgery. We studied each patient in a resting state in the early morning hours before any exertional activity such as extended walking or physical therapy. For every study, we recorded a single lead (chosen to demonstrate the P wave, usually lead II) of the electrocardiogram at a paper speed of 50 mm per second during the basal state and during atrial pacing (Bloom Associates Digital Stimulator) at twice diastolic threshold at 95, 110, 125, 140, and 155 beats per minute. We recorded the electrocardiogram after 45 seconds of pacing at each of these predetermined rates. We then discontinued pacing and allowed sinus rhythm to become re-established for about 30 seconds before reinitiating pacing at the next higher rate. When Wenckebach block occurred at one of the predetermined heart rates, or at a higher rate, we identified the cycle length at which Wenckebach periodicity occurred (hereafter termed Wenckebach CL) by repeating the pacing procedure at increments in cycle length of 10 msec until block was no longer apparent. We confirmed the Wenckebach CL by repeating the pacing procedure at 10 msec decrements in cycle length from the next lower of the predetermined heart rates. The Wenckebach CL obtained by incremental and decremental pacing corresponded within 10 msec. After completing each day's pacing series, which took approximately 25 minutes, we recorded another electrocardiogram during sinus rhythm to confirm that no change in the basal heart rate or electrocardiographic intervals had occurred during the procedure. After at least three studies over a 3 to 11 day period had established control values, each patient received digoxin orally as a loading dose of 5 μg/kg every 8 hours for the first 24 hours, then as a maintenance dose of 5-8 μg/kg per day. We repeated the pacing procedure (always just before the daily administration of digoxin) on each of at least three separate days (range, 3 to 8 days), from one to 37 days after instituting chronic digoxin.

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therapy, and obtained blood for a serum digoxin level immediately before each study. In six patients, we obtained studies after discontinuing digoxin and in one patient during and after completion of a second period of digoxin administration.

For each study we measured basal donor sinus rate and PR interval, the Wenckebach CL, and the interval from the pacing stimulus to the onset of the QRS complex (S'R interval) at each paced rate. Results in each patient from at least three studies within the control period were compared, using a one-tailed analysis of a paired Student's t-test, with results from the same number of studies in the digoxin period. In addition, the mean of all values within the control period for each patient was averaged for all patients, and compared using the same statistical analysis with the group mean within the digoxin period. Studies performed at least six days after discontinuing digoxin were used for similar analysis of results in the post-digoxin period. To determine whether our results during the digoxin period could have been influenced by enhanced leak or release of acetylcholine from postganglionic parasympathetic fibers at the A-V junction or by a modification in the level of circulating catecholamines, we made additional studies on two patients (no. 8 and 9). Serum catecholamine concentrations were measured (Upjohn Laboratories) and the Wenckebach CL determined before and after atropine 1.5 mg intravenously during control and digoxin periods. In patient 8, Wenckebach CL was determined before and after propranolol 0.1 mg/kg intravenously in each period.

All patients gave informed consent in accordance with the Stanford University Medical Committee on the Use of Human Subjects in Research before participating in the studies. No complications occurred during the investigation.

**Results**

Table 1 is a summary of the results, showing the heart rate and PR interval during sinus rhythm in the basal state, the Wenckebach CL, and the S'R interval at each of the paced heart rates during stable conditions within each of the three study periods. The mean serum digoxin concentration during the digoxin period was 1.5 ± 0.2 ng/ml (range, 0.7–2.1

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**Table 1. Summary of Variables Measured during Three Study Periods**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Basal state</th>
<th>95 (beats/min)</th>
<th>110 (beats/min)</th>
<th>140 (beats/min)</th>
<th>155 (beats/min)</th>
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<tbody>
<tr>
<td></td>
<td>Heart rate (beats/min)</td>
<td>PR interval (msec)</td>
<td>Wenckebach cycle length (msec)</td>
<td>S'R interval (msec) during pacing</td>
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<tr>
<td>1 C</td>
<td>75</td>
<td>123</td>
<td>342</td>
<td>163</td>
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<td>71</td>
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<td>441</td>
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<tr>
<td>pD</td>
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<td>2 C</td>
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<tr>
<td>D</td>
<td>74</td>
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<td>182</td>
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<tr>
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<td>86</td>
<td>150</td>
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Mean (= SEM)

| C | 81 (4) | 127 (4) | 357 (15) | 188 (7) | 199 (10) | 229 (13) | 243 (19) | 258 (23) |
| D | 80 (3) | 136 (5) | 407 (21) | 211 (18) | 229 (14) | 233 (23) | 276 (28) | 295 (27) |
| pD | NS NS .05 <.002 NS <.01 <.05 <.03 <.02 |

| pD | NS NS NS NS NS NS NS NS NS |

*Wenckebach periodicity occurred at a lower rate, preventing measurement of S'R interval.
†Basal heart rate was faster than 95 beats/min.
§Compared with control period.
¶Mean for the six patients who had measurements during three periods.
Abbreviations: S'R = duration from pacing stimulus to onset of QRS complex; C = control period; D = digoxin period; pD = post-digoxin period.
ng/ml). The serum potassium concentration remained within ±0.4 mEq/L of the mean for each patient and showed no consistent upward or downward trend within the normal range throughout the various study periods. The mean heart rate did not change during the digoxin period, whereas the mean intrinsic PR interval was slightly prolonged ($P = 0.05$). The mean Wenckebach cycle length was significantly prolonged from 357 ± 15 (SEM) msec to 407 ± 21 msec (168-147 beats/min), an increase of 14%. For every subject except one (patient 2), the mean of the values during the digoxin period was statistically greater than that during control. For each subject the percentage prolongation of the Wenckebach cycle length was plotted against the serum digoxin concentration; the resulting coordinates for all patients were related by a least squares exponential regression equation with a correlation coefficient of 0.70 (fig. 1). This relationship implies that variations in magnitude of the Wenckebach response may depend upon variations in stable serum (and presumably tissue) concentrations. At all rates above 95 beats per minute, the S'R interval was significantly prolonged during digoxin administration. Figure 2 shows basal heart rate and Wenckebach CL in patient 3 during each study period. The Wenckebach CL was significantly prolonged during digoxin administration and returned to control levels after digoxin was discontinued. Figure 3 demonstrates that both the S'R interval at 110 beats/min and Wenckebach CL became significantly prolonged during each of two digoxin periods in patient 1, and returned to control levels after digoxin was discontinued. After the second period of digoxin, measurements recorded three days after discontinuing digoxin, when the serum digoxin concentration was less than 0.2 ng/ml, were intermediate between values in the digoxin period and those at control, indicating a lag between pharmacologic effect and changes in serum concentration.

In the six patients studied after digoxin was discontinued, Wenckebach CL and S'R interval returned toward control values (table 1), suggesting that a systematic change in A-V conduction after cardiac transplantation is not responsible for the observed depression during the digoxin period.

Figure 4 shows in two patients that atropine administration had no effect on Wenckebach CL during either control or digoxin periods. Prolongation of Wenckebach CL was of the same magnitude (17% and 10%) as the mean for the whole group. Mean serum epinephrine level actually rose...
slightly from 34 pg/ml during the control period to 52 pg/ml during the digoxin period, mean serum norepinephrine level rose from 138 pg/ml to 192 pg/ml, and mean basal heart rates remained constant at 87 beats/min. Propranolol administered to patient 8, by blocking catecholamine effects upon the A-V node, caused a 10 msec (2%) prolongation over the basal measurements of Wenckebach CL during the control period and a 15 msec (3%) prolongation during the digoxin period.

Discussion

Rapid atrial pacing is an established method for examining A-V conduction,\(^{18}\) causing lengthening of the PR interval on the surface ECG. Delayed conduction through the A-V node, as measured by the atrio-His duration, is primarily responsible for lengthening of the PR interval.\(^{18}\) A progressive increase in A-V delay ultimately results in failure of transmission of one beat, thus establishing Wenckebach periodicity.\(^{19}\) Electrophysiologically, delayed conduction and dropped beats occur because of decremental conduction in nodal tissues.\(^{19}\) The status of A-V nodal conduction can be assessed by an alternative technique, the extrastimulus method,\(^{11}\) which allows evaluation of A-V nodal refractoriness. Such studies in our patients would have yielded additional information regarding the effect of chronically administered digoxin on A-V conduction. Recently, however, Bissett et al.\(^{20}\) have demonstrated a significant relationship between the functional and effective refractory periods of the A-V node and the point at which Wenckebach block occurs during rapid atrial pacing.

Our results demonstrate that prolongation of A-V conduction during pacing-induced tachycardia attends the chronic oral use of digoxin in patients whose hearts are devoid of extrinsic autonomic innervation. In every patient, the Wenckebach CL lengthened during oral digoxin administration, indicating that the A-V node became more refractory during this period. The magnitude of lengthening of the Wenckebach CL correlated significantly with the stable state serum digoxin level (fig. 1) and thus likely was dependent upon myocardial tissue levels.\(^{21}\) This relationship is analogous to that between the inotropic effect of digoxin and predicted myocardial tissue levels, as determined by Reuning et al.\(^{22}\)

The measure of A-V conduction time in our study, the S'R interval, was also lengthened at every paced rate. The S'R interval includes transmission not only through A-V nodal tissue but also through atrial muscle and His-Purkinje fibers. The direct effect of digitalis upon atrial muscle is to

![FIGURE 3. Basal heart rate, S'R interval at 110 beats/min (atrial paced), and Wenckebach cycle length for each study in patient 1. Digoxin was administered during two periods (mean serum digoxin level 0.7 and 2.1 mg/ml, respectively), and resulted in significant prolongation of S'R interval and Wenckebach period in each case (P < 0.005). The heart rate did not change significantly throughout the study. Symbols as in figure 2.](http://circ.ahajournals.org/)

![FIGURE 4. Wenckebach CL before atropine (•) and after atropine (○) during control period and digoxin period in patients 8 and 9. Serum digoxin concentration in both patients was 2.0 mg/ml. No change in Wenckebach cycle length occurred after atropine administration in either period.](http://circ.ahajournals.org/)
increase refractoriness and slow conduction\textsuperscript{7, 22} and must be considered before making conclusions about the site of delay responsible for S'R prolongation. To determine the importance of delayed conduction through the atrium in our study, we measured the interval from the paced spike to the end of the P wave (S'P interval) at the paced rate having the longest S'R interval. This S'P interval lengthened only slightly from a mean of 136 ± 12 msec during the control period to a mean of 139 ± 13 msec during digoxin. Therefore, slowed atrial conduction did not contribute significantly to the overall prolongation of the S'R interval during digoxin administration in our patients. Since we did not record intracardiac potentials in this study, we cannot determine the contribution of His-Purkinje delay to S'R interval prolongation. Results from experiments in animals indicate that large concentrations of digitalis\textsuperscript{24, 25} are necessary to impair conduction through the His-Purkinje system, although such an electrophysiologic effect may occur more readily when the frequency of stimulation is rapid.\textsuperscript{26} In man, digitalis either produces no effect on His-Purkinje conduction\textsuperscript{18} or is associated with minimal slowing, the latter manifested by ventricular aberration on the surface electrocardiogram.\textsuperscript{19} No ventricular aberration occurred at any pacing frequency in our patients. Therefore, we suggest that His-Purkinje delay probably did not account for the prolonged S'R interval, and furthermore that augmented A-V nodal delay was responsible for our findings during the digoxin period. Nevertheless, the stress of tachycardia was necessary to demonstrate the depressant action of digoxin upon A-V nodal conduction. Basal PR intervals lengthened minimally during digoxin administration, and although the S'R interval lengthened at all paced rates, this prolongation was statistically significant only at a rate of 110 beats/min or faster.

Although previous studies have suggested that postganglionic vagal fibers have no functional role in the transplanted heart,\textsuperscript{27, 28} the possibility that digoxin causes or accelerates a leak of acetylcholine from these fibers or potentiates the action of tonically-released acetylcholine must be examined to exclude vagomimetic slowing of the A-V node during the digoxin period. Since atropine did not alter Wenckebach CL during either the control period or digoxin period (fig. 4), postganglionic parasympathetic fibers are not likely to have contributed to our results.

Antiadrenergic effects of digoxin attenuate the enhanced conductivity through A-V nodal tissues produced during states of heightened sympathetic activity such as catecholamine infusions or stellate ganglion stimulation,\textsuperscript{1, 2, 6} and need to be considered as an alternative explanation of our findings. Also to be considered is the possibility that the inotropic effects of digoxin may cause a compensatory fall in systemic catecholamine activity, thereby retarding A-V conduction. Since there is no extrinsic cardiac innervation in our subjects,\textsuperscript{27, 28} adrenomedullary hormones and circulating neurotransmitters provide the major physiologic chronotropic influence upon the donor heart, and in the absence of rejection the donor rate constitutes a measure of systemic sympathoadrenal activity. In an attempt to minimize the fluctuation in levels of systemic catecholamines, we performed all studies at approximately the same time in the early morning while the patients remained in a basal state. The constancy of basal donor sinus rate in our patients throughout the study period provides evidence for overall stability of the level of circulating catecholamines at the time of each examination. Furthermore, Mendez et al.\textsuperscript{1} showed that administration of 50% of the lethal dose of acetyl-digitoxin in the presence of a level of epinephrine that would approximate 100 times the basal level in normal man\textsuperscript{29} reduced A-V nodal conduction by less than 10%. Thus, it is reasonable to assume that therapeutic levels of digoxin did not produce any important antiadrenergic influence upon A-V conduction in our resting subjects. The average increase (within the normal range) in serum catecholamine concentration in the two patients in whom these measurements were made suggests that an inotropic-induced decrease in sympathoadrenal activity during the digoxin period probably did not account for the observed depression of A-V conduction. Also, propranolol administered to one patient caused a similar decrement in A-V conduction in both control and digoxin periods, an observation compatible with similar degrees of catecholamine effect upon the A-V node in each condition.

The results of this study suggest that digoxin exerts a direct negative effect upon A-V nodal conduction in man but that a positive chronotropic stress upon the A-V node is necessary to demonstrate the effect. This conclusion contrasts with that in an earlier study from our laboratory\textsuperscript{16} which showed that acute intravenous administration of digoxin caused no significant effect upon A-V nodal refractoriness in cardiac allograft recipients, but increased both effective refractory period and functional refractory period in patients with normal cardiac innervation. Since the factors governing distribution of digoxin to the myocardium after gastrointestinal absorption and after intravenous infusion are similar, the most likely explanation for the discrepancy in results is in the temporal relationship of drug administration to examination of A-V conduction. Although serum digitoxin levels in the previous study\textsuperscript{16} were greater than 5 ng/ml when the refractory periods were determined within 60 minutes after bolus administration, tissue uptake probably was inadequate in this short interval to produce any direct pharmacologic effect. Using the data of Shapiro et al.,\textsuperscript{20} Reuning and associates\textsuperscript{27} showed that the intensity of a pharmacologic effect (i.e., the change in left ventricular ejection time index) is correlated with the predicted tissue levels of digoxin, but not with plasma levels, during distribution of the drug. Furthermore, they showed that after intravenous injection, 7 to 13 hours are required to establish a constant relationship between the amount of digoxin in the tissue compartment and the amount in the plasma compartment.\textsuperscript{22} Deutscher et al.\textsuperscript{31} also showed that peak hemodynamic effects lag behind peak myocardial digoxin concentrations after acute intravenous administration. Thus, our examination of A-V nodal conduction during chronic digoxin administration avoids the uncertainty of non-steady-state tissue concentrations and allows us to make a more valid statement about digoxin's direct action.

In conclusion, we have used the technique of rapid atrial pacing to examine A-V nodal conduction in cardiac allograft recipients sequentially during a control period, during chronic oral digoxin administration, and after discontinuing digoxin. At therapeutic serum concentrations, digoxin depressed A-V conduction under the stress of pacing-induced tachycardia. In the absence of parasympathetic
effect and alteration in circulating catecholamines, these data provide evidence for a direct (or non-neural) effect of digoxin upon the A-V node. Whether this finding has any clinical significance is unknown. The most likely setting for digoxin’s direct action to be manifested is in advanced congestive heart failure, a state of functional denervation in which parasympathetic activity is withdrawn and myocardial catecholamine stores are depleted.

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