Effects of Digoxin on Acute, Atrial Fibrillation–Induced Changes in Atrial Refractoriness

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Background—Atrial fibrillation (AF) shortens the atrial effective refractory period (ERP) and predisposes to further episodes of AF. The acute changes in atrial refractoriness may be related to tachycardia-induced intracellular calcium overload. The purpose of this study was to determine whether digoxin, which increases intracellular calcium, potentiates the acute effects of AF on atrial refractoriness in humans.

Methods and Results—In 38 healthy adults, atrial ERP was measured at basic drive cycle lengths (BDCLs) of 350 and 500 ms after autonomic blockade. Nineteen patients had been treated with digoxin for 2 weeks. After a several-minute episode of AF, atrial ERP was measured serially at alternating BDCLs. Compared with pre-AF ERPs, the first post-AF ERPs were significantly shorter in both the digoxin and the control groups ($P<0.001$). The post-AF ERP at a BDCL of 350 ms shortened to a greater degree in the digoxin group (37±16 ms) than in the control group (20±13 ms, $P<0.001$); similar changes occurred at a BDCL of 500 ms. During post-AF determinations of the atrial ERP, secondary AF episodes occurred significantly more often in the digoxin group (32% versus 16%; $P<0.04$).

Conclusions—After a brief episode of AF, digoxin augments the shortening that occurs in atrial refractoriness and predisposes to the reinduction of AF. These effects occur in the setting of autonomic blockade and therefore are more likely to be due to the effects of digoxin on intracellular calcium than to its vagotonic effects. (Circulation. 2000;102:2503-2508.)

Key Words: digoxin ■ fibrillation ■ atrium

Experimental and clinical studies have shown that atrial fibrillation (AF) shortens the atrial effective refractory period (ERP) and increases susceptibility to further episodes of AF. Verapamil has been shown to attenuate these effects of AF, which suggests that tachycardia-induced calcium overload may play a role in mediating the acute effects of AF on atrial electrophysiological properties.

Digoxin prolongs the refractory period of the AV node primarily by augmenting vagal tone, and it also has a positive inotropic effect related to an increase in intracellular calcium concentration. In a recent study, Tieleman et al demonstrated that digoxin delays recovery from AF-induced atrial electrical remodeling in goats and predisposes to the induction of AF. However, because the goats in that study were studied in the absence of autonomic blockade, it is unclear whether the potentiation of electrical remodeling was attributable to a direct or indirect effect of digoxin. Furthermore, no prior studies have examined the effects of digoxin on AF-induced electrophysiological changes in the atrium in humans. Therefore, the aim of the present study was to assess the effect of digoxin on atrial refractoriness after brief episodes of AF in humans in the presence of autonomic blockade.

Methods

Characteristics of Study Population

The subjects of this study were 38 patients referred to the University of Michigan Medical Center for radiofrequency catheter ablation of paroxysmal supraventricular tachycardia (n=36) or idiopathic ventricular tachycardia (n=2). None had a known history of AF. Exclusion criteria consisted of a baseline rhythm other than sinus rhythm, current therapy with a calcium channel antagonist or antiarrhythmic drug, and the presence of structural heart disease. Additional exclusion criteria were the induction of AF during baseline determinations of the atrial ERP and the inability to maintain a stable electrode catheter position in the right atrial appendage throughout the study protocol. In all, 7 patients were excluded because AF was induced during baseline ERP measurements, and 7 others were excluded because of the inability to maintain a stable catheter position. Among the 38 remaining subjects, there were 29 women and 9 men, and their mean age was 42±15 years (mean±SD). The mean left ventricular ejection fraction was 0.6±0.02.
Electrophysiological Testing
As part of the study protocol, 19 patients were treated with digoxin up to the day of the electrophysiology procedure. All other antiarhythmic drug therapy was discontinued at least 5 half-lives before the procedure. After informed consent was obtained, 3 quadripolar electrode catheters were inserted into a femoral vein and positioned in the right atrium. His bundle position, and right ventricular apex. Several ECG leads and the intracardiac electrograms were displayed on an oscilloscope and recorded on optical disk (EPMed-Systems). Pacing was performed with a programmable stimulator (EPMedSystems).

Study Protocol
The study protocol was approved by the Human Research Committee of the University of Michigan Medical Center and was performed on completion of the radiofrequency catheter ablation procedure, which was successful in all patients. A 6F quadripolar electrode catheter was advanced through a 63-cm sheath and positioned in the right atrial appendage so that the pacing threshold was <1.0 mA. Right atrial pressure was measured continuously through the 63-cm venous sheath. Autonomic blockade was achieved by infusion of atropine 0.04 mg/kg and propanolol 0.2 mg/kg every 5 minutes.

Nineteen patients agreed to take digoxin 0.25 mg/d for ≥14 days before the procedure. They were instructed to take the last dose of digoxin on the morning of the electrophysiology procedure. The mean serum digoxin concentration at the time of the study protocol was 1.0±0.4 ng/dL (range 0.5 to 1.9 ng/dL). The other 19 patients served as a control group, and the serum digoxin concentration was measured to be zero in each of these patients. There were no significant differences in demographic or clinical characteristics between the patients who did and did not receive digoxin.

The mean atrial pacing threshold was 0.8±0.1 mA. Pacing was performed at 3 times the threshold. Atrial ERP was measured at basic drive cycle lengths of 350 and 500 ms with drive trains of 8 beats and a 1-second pause between pacing trains. The initial S1S2 interval was set to be shorter than the ERP, and the S1S2 interval was increased in steps of 5 ms until there was atrial capture. The ERP was defined as the longest S1S2 interval that failed to result in atrial capture. The ERPs were measured after pharmacological autonomic blockade 3 times at each drive cycle length and averaged.

AF then was induced by rapid atrial pacing at cycle lengths of 180 to 210 ms. Whenever there was spontaneous conversion to sinus rhythm, rapid pacing was immediately repeated as needed to rein-duce AF. After ≥5 minutes of AF, the AF was allowed to terminate spontaneously. Electrical cardioversion was performed in 7 patients in whom the AF persisted for >10 minutes. Right atrial pressure was measured in all patients before, during, and after AF. Immediately on spontaneous or electrical cardioversion to sinus rhythm, atrial ERP was repeatedly measured at alternating basic drive cycle lengths of 350 and 500 ms. To avoid capture by the first S2, the initial S1S2 interval was very short (120 to 140 ms). The S1S2 interval was increased in steps of 5 ms until there was atrial capture. The elapsed time between resumption of sinus rhythm and each determination of the atrial ERP was measured to the nearest second with a stopwatch. The ERP was measured at alternating drive cycle lengths of 350 and 500 ms until the ERP returned to within 5 ms of the pre-AF atrial ERP or until the ERP had been measured a total of 20 times. Whenever a secondary episode of AF was unintentionally induced during measurement of the ERP, the elapsed time at which the AF occurred was noted and the duration of the episode was measured to the nearest second. In 10 patients, a secondary episode of AF persisted for >10 minutes, and electrical cardioversion was performed. In these patients, only the data collected before the onset of the persistent secondary episode of AF were used in the analysis. The ΔERP was defined as the difference between the pre-AF ERP and the first post-AF ERP.

To verify catheter stability, the pacing threshold was remeasured on completion of the study protocol. Among the 38 subjects in the study, there was ≤0.1 mA deviation from the original value. Two other patients in whom the pacing threshold increased by >0.1 mA were excluded from the study. The sinus cycle length also was remeasured on completion of the study protocol, to confirm a stable degree of autonomic blockade (Table 1).

Statistical Analysis
Continuous variables are expressed as mean±SD and were compared by a paired or Student’s t test, as appropriate. Categorical variables were compared by χ2 analysis. Pearson’s correlation coefficient (r) was used to determine the relationship between the serum digoxin concentration and ΔERP.

Polynomial growth curves or profiles were fit to the repeated measurements of atrial ERP over time in the digoxin and control groups. This methodology properly accounts for the correlation between measurements taken on the same individual over time. The analysis was restricted to the first 10 minutes after cardioversion. Parallel linear profiles in the logarithm of time were found to provide an adequate fit for the data. To test for differences in the number and duration of secondary episodes of AF, while adjusting for the correlation among observations in the same subject, nonlinear repeated-measures ANOVA was used. These statistical analyses were performed with SAS Proc Genmod and SAS Proc Mixed software. A value of P<0.05 was considered statistically significant.

Results
Pre-AF Atrial ERP
At a drive cycle length of 350 ms, the mean ERP after autonomic blockade in the digoxin group (194±14 ms) did not differ significantly from the mean ERP in the control group (199±11 ms; P=0.2). There also was no significant difference in the mean ERP between the 2 groups at a drive cycle length of 500 ms (digoxin, 206±21 ms; control, 213±12 ms; P=0.2).

Characteristics of Induced AF
The primary episode of induced AF had a mean duration of 8.1±2.6 minutes in the digoxin group and 7.6±3.0 minutes in the control group (P=0.6; Table 1). Right atrial pressure increased during AF, and there were no significant differences in right atrial pressure between the digoxin and control groups (P=0.6).

Change in ERP After AF
Both in the digoxin group and in the control group, ERP measured at drive cycle lengths of 350 and 500 ms shortened significantly after the primary episode of AF (Tables 2 and 3). Mean ΔERP was significantly greater in the digoxin group than in the control group at drive cycle lengths of both 350 ms (37±16 versus 20±13 ms, P<0.001) and 500 ms (35±18
versus 20±15 ms, \( P=0.001 \)). There was no relationship between serum digoxin concentration and ΔERP at a drive cycle length of either 350 ms (\( r=0.03, P=0.9 \)) or 500 ms (\( r=0.1, P=0.7 \)).

### Temporal Recovery of Atrial ERP

In the control group, ERP at a drive cycle length of 350 ms returned to a value that did not differ significantly from pre-AF ERP by 7.7±4.0 minutes after conversion of the primary episode of AF. In the digoxin group, atrial ERP at 10 minutes after conversion of the primary episode of AF was still shorter than the pre-AF value. The ERP temporal recovery curves in the digoxin and control groups differed significantly at a drive cycle length of 350 ms (\( P<0.001 \); Figure 1) and 500 ms (\( P=0.03 \); Figure 2).

In 6 patients in the digoxin group and 9 in the control group, no secondary episodes of AF were induced. In these patients, there were no differences in the temporal recovery of atrial ERP between the digoxin and control groups at a drive cycle length of either 350 ms (\( P=0.2 \)) or 500 ms (\( P=0.8 \)).

### Induction of Secondary Episodes of AF

In the digoxin group, a secondary episode of AF was induced during 92 (32%) of 292 measurements of the ERP in 13

### TABLE 3. Changes in Atrial ERP at Basic Drive Cycle Length of 500 ms After Conversion of First Episode of AF

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>ERP, ms</th>
<th>P vs Pre-AF ERP</th>
<th>Time After AF Conversion, min</th>
<th>No. of Patients</th>
<th>ERP, ms</th>
<th>P vs Pre-AF ERP</th>
<th>Time After AF Conversion, min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-AF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>206±21</td>
<td></td>
<td></td>
<td>19</td>
<td>213±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-AF measurement No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>17</td>
<td>171±22</td>
<td>&lt;0.001</td>
<td>19</td>
<td>192±20</td>
<td>&lt;0.001</td>
<td>3.0±4.5</td>
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<tr>
<td>2</td>
<td>16</td>
<td>181±21</td>
<td>&lt;0.001</td>
<td>18</td>
<td>197±22</td>
<td>&lt;0.01</td>
<td>4.5±4.8</td>
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<tr>
<td>3</td>
<td>14</td>
<td>190±21</td>
<td>0.02</td>
<td>17</td>
<td>201±15</td>
<td>&lt;0.01</td>
<td>5.4±4.9</td>
</tr>
<tr>
<td>4</td>
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<td>191±20</td>
<td>0.02</td>
<td>15</td>
<td>200±16</td>
<td>&lt;0.01</td>
<td>5.7±3.8</td>
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<tr>
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<td>193±23</td>
<td>0.05</td>
<td>15</td>
<td>201±14</td>
<td>&lt;0.01</td>
<td>7.0±4.2</td>
</tr>
<tr>
<td>6</td>
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<td>193±26</td>
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<td>202±15</td>
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<td>14</td>
<td>193±30</td>
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</tr>
<tr>
<td>8</td>
<td>14</td>
<td>197±24</td>
<td>0.12</td>
<td>11</td>
<td>205±13</td>
<td>0.04</td>
<td>9.2±4.5</td>
</tr>
<tr>
<td>9</td>
<td>14</td>
<td>197±25</td>
<td>0.12</td>
<td>10</td>
<td>204±15</td>
<td>0.04</td>
<td>10.1±4.8</td>
</tr>
<tr>
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<td>199±23</td>
<td>0.18</td>
<td>9</td>
<td>209±16</td>
<td>0.25</td>
<td>9.8±3.3</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SD.
(68%) of 19 patients. In the control group, a secondary episode of AF was induced during 43 (16%) of 277 measurements of the ERP \( (P<0.04 \text{ compared with digoxin group}) \) in 10 (53%) of 19 patients \( (P=0.3 \text{ compared with the digoxin group}) \). The mean duration of secondary episodes of AF was 1.2±2.9 minutes in the digoxin group and 1.3±3.2 minutes in the control group \( (P=0.8) \).

The incidence of secondary episodes of AF progressively diminished as the elapsed time from the primary episode of AF lengthened. During the first post-AF measurement of the atrial ERP, 68% of the ERP measurements in the digoxin group and 53% in the control group resulted in a secondary AF episode. The mean duration of these episodes was 250±328 seconds in the digoxin group and 225±358 seconds in the control group \( (P=0.9) \). Eight minutes after conversion of the primary episode of AF to sinus rhythm, 21% of the ERP measurements in the digoxin group and 17% in the control group resulted in a secondary episode of AF. The mean duration of these episodes was 7±7 seconds in the digoxin group and 6±2 seconds in the control group \( (P=0.8) \).

When the digoxin and control groups were compared, there were no significant differences in the progressive decrease in vulnerability or in the duration of secondary AF episodes \( (P=0.8; \text{ Figure 3}) \).

**Discussion**

**Main Findings**

The results of this study demonstrate that the acute effects of a several-minute episode of AF on the electrophysiological properties of the atrium are accentuated by digoxin. Digoxin resulted in a greater degree of shortening of the atrial ERP after a brief episode of AF and enhanced the heightened predisposition toward the reinduction of AF that was observed on conversion to sinus rhythm. Temporal recovery from the acute effects of AF was manifest as a progressive increase in the atrial ERP, and in patients treated with digoxin, recovery from the effects of AF was delayed. However, the delay in recovery of the ERP was attributable to the confounding effects of secondary episodes of AF on atrial refractoriness, because no significant delay in temporal recovery was observed in the digoxin group when the analysis was restricted to subjects who did not have secondary episodes of AF.

The effects of digoxin were demonstrated in the setting of pharmacological autonomic blockade, which indicates that they cannot be attributed to the vagotonic properties of digoxin.

**Mechanism of the Effects of Digoxin**

Digoxin increases the intracellular sodium concentration by directly inhibiting the sarcolemmal Na\(^+\)/K\(^+\)-ATPase pump.\(^{10}\) An increase in the intracellular sodium concentration drives the Na\(^+\)/Ca\(^2+\) exchanger, resulting in an increase in the intracellular calcium concentration, which accounts for the positive inotropic effect of digoxin.\(^7\) An elevated intracellular calcium concentration during AF shortens the action potential duration,\(^2\) probably because of negative feedback on L-type calcium channel activity and a shortening of the plateau phase of the action potential,\(^11\) augmentation of the transient outward potassium current, \(I_{to}\),\(^{12}\) and enhancement of the de-
layed rectifier current, $I$. The resultant decrease in atrial refractoriness favors the occurrence of AF due to multiple-wavelet reentry.

Digoxin also has a vagotonic effect, which shortens the atrial action potential duration, the atrial ERP, and the atrial wavelength and which causes a nonuniform reduction in conduction velocity, resulting in a heightened predisposition to AF. In the present study, the vagotonic effects of digoxin were minimized by pharmacological autonomic blockade.

Prior Experimental Studies

Recently, Tieleman et al demonstrated that atrial electrophysiological remodeling caused by pacing-induced tachycardia in goats was potentiated by digoxin. In addition, digoxin delayed the recovery from the effects of tachycardia. These findings are qualitatively similar to the findings of the present study. However, the temporal aspects of the 2 studies are notably different. In the prior study in goats, rapid AV pacing was performed for 24 hours, but in the present study, episodes of AF were only several minutes in duration. Therefore, whereas the duration of rapid pacing and AF in the prior study was long enough to result in electrical remodeling that took at least 1 day to reverse, the episodes of AF in the present study were not long enough to induce a remodeling process in the atrium. Electrical remodeling in the atrium may be attributable to changes in gene expression, which take hours to occur and to dissipate. In contrast, it is likely that the effects of a short episode of AF in the present study were caused by acute activation of potassium currents and/or changes in intracellular calcium concentration, which dissipate over a period of minutes.

Prior Clinical Studies

The results of this study suggest that digoxin may facilitate or promote short-term recurrences of AF among patients in whom it is used to control the ventricular rate. This possibility seems at odds with the widespread use of digoxin in patients who have AF. However, few studies have attempted to quantify the effect of digoxin on the incidence of AF. In a randomized study conducted in patients who underwent coronary artery bypass surgery, the effects of digoxin and placebo on the incidence of postoperative AF were compared. AF was found to occur significantly more often in the digoxin group (27.8%) than in the placebo group (11.4%; $P<0.05$). The results of the present study may provide an explanation for why AF is more likely to occur or recur among patients treated with digoxin.

Although the results of the present study suggest the potential for a deleterious clinical effect of digoxin among patients with AF, such an effect may be difficult to recognize clinically or may be masked by the concomitant use of other medications such as verapamil or class 1 or III antiarrhythmic drugs. For example, in a double-blinded, placebo-controlled study on the effect of digoxin on symptomatic recurrences of paroxysmal AF, a small reduction in the frequency of symptomatic episodes of AF was demonstrated in the digoxin group. However, this beneficial clinical effect of digoxin may have been attributable to a reduction in ventricular rate and irregularity as opposed to a reduction in the number of AF episodes.

It is clear that further clinical studies are needed to demonstrate whether the proarrhythmic atrial electrophysiological effects of digoxin found in this and prior studies are clinically relevant.

Study Limitations

A limitation of this study is that the ERP was measured only at 1 site in the right atrium, and therefore the effects of pacing-induced AF and digoxin on refractoriness in other areas of the atrium or on heterogeneity of refractoriness remain unknown. A second limitation is that the findings may be specific to pacing-induced AF in subjects with structurally normal atria and no prior history of AF and may not apply to spontaneous episodes of AF or to episodes of AF that occur in patients with structurally abnormal atria. A third limitation is the wide range of serum digoxin concentrations among the patients in the digoxin group, which may have resulted in underestimation or overestimation of the effects of digoxin in some patients. However, this possibility seems unlikely because there was no relationship between serum digoxin concentration and ERP.

Conclusions

In conclusion, digoxin potentiates the shortening of atrial ERP and predisposition toward further episodes of AF that occurs after a short episode of AF. Digoxin already has been recognized as exerting a potentially deleterious effect in patients who have the vagotonic type of paroxysmal AF. The results of the present study suggest that digoxin may facilitate or promote early recurrences of AF after conversion to sinus rhythm not only in patients with vagotonic AF but also among the general population of patients with AF.

Acknowledgments

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References

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