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Circulation. 1999;100:1836-1842
doi: 10.1161/01.CIR.100.17.1836

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

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Digoxin Delays Recovery From Tachycardia-Induced Electrical Remodeling of the Atria

Robert G. Tieleman, MD; Yuri Blaauw, MD; Isabelle C. Van Gelder, MD, PhD; Cees D.J. De Langen, PhD; Pieter J. de Kam, MSc; Jan G. Grandjean, MD, PhD; Kornelis W. Patberg, MD; Klaas J. Bel, BSc; Maurits A. Allessie, MD, PhD; Harry J.G.M. Crijns, MD, PhD

Background—Atrial fibrillation (AF) induces electrical remodeling, which is thought to be responsible for the low success rate of antiarrhythmic treatment in AF of longer duration. Electrical remodeling seems to be related to tachycardia-induced intracellular calcium overload. Due to its vagomimetic action, digoxin is widely used to control the ventricular rate during AF, but it also increases intracellular calcium. On the basis of these characteristics, we hypothesized that digoxin would aggravate tachycardia-induced electrical remodeling.

Methods and Results—We analyzed the atrial effective refractory period (AERP) at cycle lengths of 430, 300, and 200 ms during 24 hours of rapid atrio/ventricular (300/150 bpm) pacing in 7 chronically instrumented conscious goats treated with digoxin or saline. Digoxin decreased the spontaneous heart rate but had no other effects on baseline electrophysiological characteristics. In addition to a moderate increase in the rate of electrical remodeling during rapid pacing, digoxin significantly delayed the recovery from electrical remodeling after cessation of pacing (at 430, 300, and 200 ms: $P<0.001$, $P=0.0015$, and $P=0.007$, respectively). This was paralleled by an increased inducibility and duration of AF during digoxin. Multivariate analysis revealed that both a short AERP and treatment with digoxin were independent predictors of inducibility ($P=0.001$ and $P=0.03$, respectively) and duration ($P=0.001$ for both) of AF.

Conclusions—Digoxin aggravates tachycardia-induced atrial electrical remodeling and delays recovery from electrical remodeling in the goat, which increases the inducibility and duration of AF.

Key Words: fibrillation ■ pacing ■ remodeling ■ digoxin ■ calcium ■ nervous system, autonomic

Atrial fibrillation (AF) leads to shortening of the atrial refractory period with loss of the physiological rate-related shortening, which results in an increased susceptibility for the development of persistent AF, as was shown by Wijffels et al in chronically instrumented goats. The mechanism behind this so-called electrical remodeling of the atria by AF has not yet been clarified. However, tachycardia-induced intracellular calcium overload may be an important factor, because verapamil administered during rapid atrial pacing reduced electrical remodeling in goats, and humans, whereas hypercalcemia decreased the recovery from electrical remodeling in dogs.

Digoxin is the oldest and most frequently used drug in AF for control of the ventricular rate. During AF, the negative chronotropic action of digoxin is due to prolongation of the refractory period of the AV node, mainly because of augmentation of the vagal tone. Digoxin also inhibits the sarcoplasmal Na,K-ATPase pump, resulting in an increased concentration of intracellular sodium, which activates the concentration-dependent Na/Ca exchanger. As a result, the intracellular calcium concentration increases. On the basis of these characteristics, we hypothesized that digoxin may have deleterious effects on atrial electrical remodeling during atrial tachycardia. The aim of the present study was to investigate the effect of digoxin on pacing-induced electrical remodeling of the atria in chronically instrumented goats.

Methods

Animal Model and Electrophysiological Measurements

In general, the animal model and methods were similar to those described earlier. In short, in 9 goats weighing 48±9 kg, atrial and ventricular electrodes were implanted. Rapid atrio/ventricular (300/150 bpm) pacing was performed for a period of 24 hours, after which sinus rhythm was allowed to resume to study recovery from electrical remodeling for 24 hours. During these 2 days, we measured the atrial effective refractory period (AERP) at cycle lengths (CLs) of 430, 300, and 200 ms by programmed electrical stimulation and determined the conduction velocity, Wenckebach point, and ECG intervals at 4- to 8-hour intervals as described previously. Dispersion of refractoriness was defined as the longest minus the shortest.
AERP. Inducibility of AF was defined as the relative number of pacing sites at which episodes of rapid irregular atrial activity lasting >1 second was induced by a single extrastimulus.

Heart Rate Variability and Autonomic Nervous Tone in Goats
Before rapid atrioventricular (AV) pacing and ~10 minutes after interruption of pacing during each data sampling point, 500 AA intervals were recorded to determine parameters of heart rate variability (Table 1) by standard techniques described elsewhere,9 which were recently validated in goats.10

Digoxin Administration
In each goat, the pacing protocol was performed both during treatment with digoxin and during control saline infusion. Digoxin or saline infusion was started 2 hours before rapid atrial pacing. Digoxin administration was started with a loading dose of 0.5 mg, followed by 0.5 mg at t=4 and t=24 hours. Digoxin plasma levels were measured by venous sampling ≥6 hours after bolus infusion. A minimal interval of 1 week was maintained before the protocol was repeated. Digoxin and control experiments were performed in random order. To define a dose-effect relation, the dose of digoxin was doubled in 2 goats. Unfortunately, these goats died of ventricular fibrillation before the second dose of digoxin. Because no control experiments had been performed yet, the incomplete data from these goats were excluded from the final analysis.

Statistical Analysis
Analysis was performed with the individual electrodes used as the experimental units. Only the atrial sites at which determination of the AERP was performed both during control and during digoxin were used for statistical analysis. Data are reported as mean±SEM unless stated otherwise. A 2-sided probability level of p=0.05 was considered significant. For comparison of continuous variables, Student’s t test or the Wilcoxon rank-sum test was used. To evaluate differences between groups of discrete variables, a 2-tailed Fisher’s exact test was used. Bonferroni’s correction was used in case of multiple comparisons. Time series were analyzed by repeated measurements, by use of a random coefficient model. Multivariate regression analysis was performed to determine the parameters related to inducibility and duration of AF. The analysis was performed with SAS statistical software (SAS, version 6.12).

Results
Electrophysiological Effects of Digoxin
Before pacing was started, digoxin significantly increased the average AA interval from 563±43 ms to 634±52 ms (p<0.001) and caused a nonsignificant increase of the Wenckebach point from 242±20 ms to 277±39 ms. Digoxin had no effect on the baseline AERP (CL 430, from 141±9 ms to 138±9 ms; CL 300, from 150±6 ms to 149±8 ms; CL 200, from 132±5 ms to 133±5 ms), dispersion of refractoriness (CL 430, from 41±10 ms to 46±7 ms), conduction velocity (CL 430, 1.4±0.4 ms to 1.5±0.4; CL 300, 1.3±0.4 ms to 1.3±0.3), or any of the ECG parameters other than heart rate.

As shown in Figure 1, during the 2 days of the experiments, the average spontaneous AA interval as calculated from the individual values at each data sampling point during the digoxin experiments was consistently longer than in the control experiments (665±56 ms versus 614±53 ms, p<0.001). This was paralleled by a small but significant increase of the average Wenckebach point during the digoxin experiments compared with control (317±16 ms versus 295±18 ms, p<0.05).

In both the control and digoxin experiments, no significant changes were demonstrated in spontaneous heart rate, QRS duration, and PQ or QT interval during the 24 hours of rapid pacing. In both groups, however, there was a decreased heart rate during the 24 hours after cessation of pacing, ie, during day 2, compared with the spontaneous heart rate during day 1 (change in mean AA-interval control, from 583±54 ms to 633±61 ms, p<0.001; digoxin, from 634±57 ms to 704±77 ms, p<0.001). The average plasma level of digoxin during the experiments was 0.9±0.3 μg/L.

Digoxin and Vagal Tone
The vagomimetic effect of digoxin was examined by analysis of heart rate variability. Apart from the decreased heart rate during digoxin, there were no significant differences in the mean values of heart rate variability parameters between the control and digoxin experiments (rMSSD, 42±18 ms; LF/HF, 4.3±1.1 ms2; LnLF, 5.7±1.7 ms2; LnTP, 6.2±2.1 ms2; Hedin et al. Annals of Internal Medicine 19, 1138-1144, 1973. P<0.001).

Table 1. Definition of Time Domain and Frequency Domain Heart Rate Variability Parameters Used to Assess Autonomic Modulation of the Heart Rate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AvgNN (ms)</td>
<td>The mean of all normal-to-normal AA intervals</td>
</tr>
<tr>
<td>rMSSD (ms)</td>
<td>Root mean square of successive differences: square root of the mean of the squared differences between successive normal intervals</td>
</tr>
<tr>
<td>LnHF (ms2)</td>
<td>Natural logarithm of high-frequency power; power spectrum between 0.15 and 0.40 Hz</td>
</tr>
<tr>
<td>LnLF (ms2)</td>
<td>Natural logarithm of low-frequency power; power spectrum between 0.04 and 0.15 Hz</td>
</tr>
<tr>
<td>LnTP (ms2)</td>
<td>Natural logarithm of total power; power spectrum between 0.04 and 0.40 Hz</td>
</tr>
<tr>
<td>LF/HF</td>
<td>Fraction of low-frequency and high-frequency power</td>
</tr>
</tbody>
</table>

Figure 1. Decrease in heart rate during digoxin experiments compared with control (p<0.001). In both treatment groups, AA intervals after cessation of pacing were significantly prolonged compared with day 1 (average AA interval day 1 vs day 2: P<0.001 for both).
TABLE 1. Changes in the AERP (mean±SD) During Rapid Atrial Pacing in 7 Goats During Saline and Digoxin

<table>
<thead>
<tr>
<th>BCL</th>
<th>t=0</th>
<th>t=24</th>
<th>t=24SR</th>
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<td>300</td>
<td>161±17</td>
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<td>147±21</td>
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<td>125±13</td>
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<td>119±27</td>
</tr>
<tr>
<td>300</td>
<td>130±17</td>
<td>91±18</td>
<td>133±28</td>
</tr>
<tr>
<td>430</td>
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<td>107±27</td>
</tr>
<tr>
<td>200</td>
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<td>90±10</td>
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<td>158±14</td>
<td>90±5</td>
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<tr>
<td>430</td>
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</tr>
<tr>
<td>430</td>
<td>140±23</td>
<td>92±23</td>
<td>122±35</td>
</tr>
</tbody>
</table>

n indicates number of electrodes; BCL, basic cycle length; and SR, sinus rhythm.

Effects of Digoxin on Electrical Remodeling

The AERP was measured at 6.9±1.4 atrial sites. Table 2 shows the average AERP at each CL in the individual goats. During the 24 hours of rapid pacing, the AERP shortened significantly at all 3 CLs but more at the longer CLs, resulting in loss of rate adaptation of the AERP, both in the digoxin experiments and during control (Figure 2). The time course of remodeling was calculated for each site at which the AERP was measured, with the random-coefficient model used for repeated measurements. It was characterized by the following function: AERP = AERP_0 + τ×Ln(t), where t is time (hours), Ln is natural logarithm, and τ is the time constant of remodeling. Figure 3 shows the average time course of remodeling at CLs of 430, 300, and 200 ms. During digoxin, the rate of AERP shortening was slightly but significantly increased compared with the control experiments at a CL of 200 and 300 ms but not at 430 ms.

Recovery From Electrical Remodeling After Restoration of Sinus Rhythm

After termination of rapid AV pacing, the AERP gradually prolonged (Figure 4). The time course of recovery from ms^-1; LF/HF, 7.6±6.0 versus 6.8±5.5, respectively, P = NS for all). (See Table 1 for definitions.) Conversely, in addition to the decreased heart rate during day 2 of the experiment (Figure 1), there also was a significant increase of the mean LnHF in the digoxin experiments (from 4.2±1.1 to 5.2±1.3, P < 0.001) and in the control experiments (from 3.8±1.1 to 4.9±1.4, P < 0.001). This indicates an increase in vagal modulation of the heart rate after cessation of pacing in both treatment groups, with no significant difference in the LnHF between the digoxin and control experiments.
electrical remodeling was characterized by the function
\[ \text{AERP} = a \times (t-24) + b, \]
where \( t \) is time (hours), \( a \) is the time constant of recovery from electrical remodeling, and \( b \) is the intercept with the \( y \) axis at \( t=24 \) hours. In the digoxin experiments, recovery from electrical remodeling started at a lower AERP and progressed at a slower pace than recovery during the control experiments, thereby increasing the time until normalization of the refractory period.

**Conduction Velocity and Dispersion of Refractoriness**

The intra-atrial conduction velocity before \((t=0)\) and after \((t=24)\) rapid atrial pacing did not change in either the control (CL 430 ms: 1.3±0.3 versus 1.3±0.4 m/s, \( P = \text{NS} \); CL 200 ms: 1.2±0.4 versus 1.2±0.5 m/s, \( P = \text{NS} \)) or the digoxin experiments (CL 430 ms: 1.5±0.4 versus 1.4±0.4 m/s, \( P = \text{NS} \); CL 200 ms: 1.3±0.3 versus 1.4±0.4 m/s, \( P = \text{NS} \)). After 24 hours of rapid atrial pacing, there was a trend toward a decrease in dispersion of refractoriness in both treatment groups \((t=0 \text{ versus } t=24): \text{CL 430 ms: control, from } 44±7 \text{ to } 37±8 \text{ ms; digoxin, from } 46±7 \text{ to } 32±8 \text{ ms}). Twenty-four hours after cessation of pacing, the dispersion had increased again in both treatment groups (CL 430 ms: control, 49±9 ms; digoxin, 48±10 ms). However, these changes did not reach statistical significance.

**Determinants of Inducibility and Duration of AF**

Digoxin increased the inducibility of AF (Figure 5), and the median duration of AF episodes was also slightly increased, although there was a severely skewed distribution and a large overlap between the 2 treatment groups (Figure 6). Using multivariate regression analysis, we analyzed the individual contributions of dispersion of refractoriness, AERP, and treatment group on the inducibility and duration of AF. A short AERP and treatment with digoxin both independently contributed to the inducibility \((P<0.001, P=0.03, \text{ respectively})\) and the duration \((P<0.001 \text{ for both})\) of AF. Dispersion of refractoriness was not an independent predictor of the inducibility or duration of AF.

**Discussion**

**Main Results**

This study demonstrated a slight increase in the rate of remodeling during rapid atrial pacing and a pronounced delay in the recovery from atrial electrical remodeling by digoxin. This was paralleled by an increase in inducibility and duration of AF during the digoxin experiments.

**Electrophysiological Effects of Digoxin**

Digoxin exerts its action on cardiac tissue through 2 independent pathways. First, it has a direct effect through inhibition of the ATP-ase–dependent Na/K pump.\(^{11}\) The subsequent increase in intracellular sodium will activate the Na/Ca exchanger, leading to increased levels of intracellular calcium, which is responsible for the positive inotropic action of digoxin.\(^7,8\) The second, indirect mechanism by which digoxin has an effect on the myocardium is augmentation of the cardiac vagal tone through central and peripheral effects.\(^6\) The balance between the direct and indirect effects may be dependent on the serum concentration of the cardiac glycoside in such a way that the indirect effect becomes more prominent during the elimination phase after a single bolus, although this was demonstrated only for digitoxin, but not digoxin.\(^12\) Therefore, we used repeated administration of digoxin, resulting in stable-state serum concentrations, to prevent dissociation of these effects during our experiments.

Digoxin has different electrophysiological effects on various cardiac tissues. The sinus node responds to therapeutic doses of digoxin with a lower spontaneous depolarization frequency,\(^{13,14}\) whereas digoxin increases the refractory period and decreases the conduction velocity of the AV node.\(^14\) In the present study, the decreased heart rate during digoxin was accompanied by a moderate prolongation of the Wenckebach point but no change in the PR interval.

In vitro experiments have shown that digoxin decreases the refractory period of atrial tissue,\(^{13,14}\) an effect that can be blocked by atropine.\(^13\) In humans, however, acute intravenous injection of digitalis resulted in either no change\(^15\) or an increase in the refractory period,\(^16,17\) with inconsistent...
changes in intra-atrial conduction velocity. It is therefore suggested that therapeutic doses of digitalis may not exert much parasympathomimetic effect on the atrial myocardium in conscious humans. Similarly, in the present study there was no effect of digoxin on the baseline atrial refractory period. Further evidence for a minor role of vagal augmentation was that in our conscious goats, digoxin did not significantly increase heart rate variability.
Direct Effect of Digoxin and Atrial Electrical Remodeling

Because verapamil reduces atrial electrical remodeling and hypercalcemia reduces recovery from electrical remodeling, it is suggested that electrical remodeling is due to intracellular calcium overload, at least during the first 24 hours of atrial tachycardia. Yue et al gave further support to the role of calcium by demonstrating that 6 weeks of rapid atrial pacing in dogs led to a significant decrease in \( I_{Ca} \) density, which was accompanied by a reduced action potential duration and loss of the physiological adaptation to heart rate. Considering the high rate of calcium inflow during tachycardia, it is conceivable that in our experiments, inhibition of the Na,K-ATPase pump by digoxin does not substantially augment tachycardia-induced electrical remodeling, similar to the findings during hypercalcemia.

After cessation of pacing, removal of the excess intracytosolic calcium is needed for a reversal of the ionic changes that are responsible for electrical remodeling. Under normal conditions, the 2-directional, concentration-dependent Na/Ca exchanger is mainly responsible for the diastolic “washout” of calcium. Therefore, hypercalcemia, which creates an increased calcium concentration in the extracellular space, hampers the efflux of cytosolic calcium. As mentioned before, digoxin inhibits the Na,K-ATPase pump, which results in an increase in intracellular sodium. This increased sodium concentration competes with calcium for binding to the receptor on the Na/Ca exchanger, thereby decreasing calcium efflux. Therefore, by maintaining an elevated cytosolic calcium concentration during the recovery from electrical remodeling, digoxin delays normalization of channel function and hence refractoriness, similar to hypercalcemia in the experiments by Goette at al. The direct effect of digoxin can also explain the increased inducibility and duration of AF and the 2 accidental inductions of ventricular fibrillation in the double-dose digoxin experiments by increasing calcium-dependent automaticity and triggered activity, as was shown in vitro by Hordof et al.

Vagomimetic Effect of Digoxin and Electrical Remodeling

A vagomimetic effect of digoxin may also have contributed to the findings of the present study. This was recently suggested by analysis of heart rate variability during recovery from electrical remodeling performed in our laboratory according to the same experimental protocol in a larger number of goats without medication. In that study, we found that in goats with a high vagal tone (as indicated by a high LnHF), recovery from electrical remodeling was significantly less than in goats with a low vagal tone. A vagomimetic effect of digoxin, therefore, may reduce recovery from electrical remodeling. In the present study, however, digoxin did not significantly increase the LnHF compared with control. Furthermore, digoxin resulted in only a moderate increase in the average AA interval and Wenckebach point, without significant changes in the duration of the PR interval, baseline AERP, or dispersion of refractoriness. Therefore, augmentation of vagal tone by digoxin may be of limited value in explaining the effects of digoxin on the refractory period.

Time Course of Recovery From Electrical Remodeling

An exponential prolongation of the AERP after cessation of rapid pacing could have been expected, because Olsson et al described an exponential prolongation of monophasic action potentials immediately after cessation of high-rate pacing or cardioversion of AF. In a previous study in dogs, as well as in the present study, however, recovery from electrical remodeling was a linear process. The fundamental difference from the study by Olsson et al is that they examined the early functional (metabolic) adaptation of the monophasic action potential duration to a slower heart rate, with 50% of the action potential prolongation occurring within 3 to 7 minutes after cessation of tachycardia. In our experiments, we investigated more structural adaptation, possibly due to changes in genetic makeup and channel expression in the cells, because we did not start to measure refractory periods until \( \approx 15 \) minutes after cessation of pacing.
Clinical Implications
The findings of the present study indicate that digoxin theoretically may increase the chance of a recurrence of AF after restoration of sinus rhythm by attenuating the recovery from electrical remodeling of the atria. In contrast, in previous studies it was shown that the L-type calcium channel blocker verapamil could reduce electrical remodeling of the atria.2–4 The effects of medication administered during AF on maintenance of sinus rhythm after electrical cardioversion have recently been investigated by our group in an observational, nonrandomized study. We showed that patients treated with intracellular calcium—lowering drugs during AF experienced significantly fewer recurrences after AF cardioversion, whereas among patients who had a relapse of AF, significantly more were on monotherapy with digoxin.22 The results of the present study, together with the previous studies, may bear important consequences for the therapy of AF, because they suggest that digoxin may be less preferable for rate control in patients with AF in whom future restoration of sinus rhythm is still an option. They encourage the initiation of clinical trials to evaluate the possible harm done by digoxin on the arrhythmia prognosis in patients with atrial tachycardias or AF.

Limitations of the Study
In the present study, electrical remodeling was induced by rapid atrial pacing at approximately half the depolarization rate as during AF. Although this resulted in a similar rate of remodeling as during AF,1 it cannot be excluded that during AF, digoxin has a different effect.

Furthermore, to study the effects of digoxin on atrial electrophysiology, irrespective of the ventricular rate, the ventricles were paced in a 2:1 mode at a rate of 150 bpm. Therefore, digoxin could not exert its rate-controlling effect during atrial pacing. In case digoxin is administered during AF in the clinical situation, the reduction in ventricular rate may be indirectly beneficial for the atrial electrophysiology. This could reduce the demonstrated detrimental effects of digoxin in this study.

To study a dose-response relationship of the effect of digoxin on (recovery from) electrical remodeling, we administered 2 different doses of digoxin. However, doubling the dose of digoxin resulted in fatal ventricular fibrillation during rapid AV pacing and therefore could not be performed safely. Finally, because atropine was not administered, we were not able to distinguish between direct and indirect effects of digoxin. Conversely, as we discussed, both of these mechanisms could explain our findings.

Acknowledgment
Dr Van Gelder was supported by grant 94.014 of the Netherlands Heart Foundation, Den Haag, The Netherlands.

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