The Cellular Electrophysiologic Effects of Digitalis on Human Atrial Fibers

ALLAN J. HORDOF, M.D., ALAN SPOTNITZ, M.D., LUC MARY-RABINE, M.D., RICHARD N. EDIE, M.D., AND MICHAEL R. ROSEN, M.D.

SUMMARY We used microelectrode techniques to study the indirect and direct actions of ouabain on human atrial fibers (HAF) obtained from patients with congenital heart disease undergoing open heart surgery. At 15 min of superfusion ouabain, 2 × 10⁻⁶M, induced an increase in maximum diastolic potential (MDP), action potential (AP) amplitude and upstroke velocity of phase 0 depolarization (Vmax) and a decrease in AP duration. Spontaneously beating HAF showed a decrease in automaticity. Acetylcholine (3 × 10⁻⁴M) induced identical effects on AP characteristics and automaticity. Prior treatment with atropine (1 × 10⁻⁴M) blocked these effects of ouabain and acetylcholine. Superfusion with ouabain (2 × 10⁻⁷M) for 30 to 90 min resulted in decreased MDP, AP amplitude and Vmax, and a further decrease in AP duration. Phase 4 depolarization and spontaneous rate increased and delayed afterdepolarization and tachyarrhythmias occurred. The ACh-like effects of digitalis decrease automaticity and increase MDP of HAF; the direct effects decrease MDP, increase automaticity, and induce tachyarrhythmias.

STUDIES OF DIGITALIS EFFECTS on mammalian atria have shown that low drug concentrations tend to slow sinus rate, whereas high concentrations induce ectopic pacemaker function and tachyarrhythmias. Toda and West1 demonstrated that ouabain, 2 × 10⁻⁴M, augments the negative chronotropic response to vagal stimulation and to acetylcholine of rabbit sinus node. With higher concentrations of ouabain (1 × 10⁻⁴M) the negative chronotropic responses to vagal stimulation and to exogenous acetylcholine application were inhibited. Ten Eick and Hoffman2 showed that the negative chronotropic effect of digitalis on rabbit sinus node was mediated primarily through the parasympathetic nervous system and was not the result of direct effects of the drug on the sinus node. The effects of ouabain were blocked by prior treatment with atropine. These investigators also demonstrated that digitalis increases the number of vagal fibers responding to a constant strength stimulus and enhances the effects of the treatment alpha,- the sinus node by increasing nerve excitability.3

Studies done in intact animals also have shown that vagal afferent and efferent pathways must be intact for ouabain to exert its negative chronotropic effect on the sinus node.4,5 Whereas the effects of low concentrations of digitalis appear to be mediated through the autonomic nervous system, the actions of higher or toxic concentrations have been attributed to a direct effect on cardiac fibers.6,7 The toxic effects of digitalis on mammalian atrial fibers include decreases in membrane potential and action potential amplitude, increases in automaticity, and the occurrence of delayed afterdepolarizations.8

The purpose of the present study was to investigate the therapeutic and toxic effects of digitalis on fibers obtained from diseased and from relatively healthy human right atria. In so doing, we intended to identify the cellular electrophysiologic mechanisms whereby 1) therapeutic digitalis concentrations may improve atrial electrophysiologic function and thereby suppress arrhythmias and 2) toxic concentrations may induce atrial arrhythmias.

Methods

Specimens of right atria were obtained from the hearts of 20 patients undergoing open heart surgery for treatment of congenital heart disease. The patients’ ages ranged from 2-15 years (mean, 6.5 years). Their diagnoses are described below. None of the patients had received digoxin or an an-

From the Departments of Pediatrics, Pharmacology, and Surgery, Columbia University College of Physicians and Surgeons, New York, New York. Supported in part by USPHS-NHLBI grants HL-12738 and HL-17766 and a grant from the Irma T. Hirschl Foundation.

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Address for reprints: Allan J. Hordof, M.D., Department of Pediatrics, Columbia University College of Physicians and Surgeons, 630 West 168th Street, New York, New York 10032.

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tiarrhythmic drug within 24 hours of surgery. None had been treated at any time with digitalis leaf or digitoxin.

Prior to surgery informed consent was obtained. At surgery, during the routine cannulation procedure for cardiopulmonary bypass, approximately 1 cm² of myocardium was removed from the anterior free wall of the right atrium and immediately immersed in iced Tyrode's solution¹⁰ having a potassium concentration ([K⁺])₃ = 4 mM. The tissue was transported rapidly to the laboratory and transferred to a Lucite tissue chamber in which it was superfused with Tyrode's solution, warmed to 37°C, and equilibrated with 95% O₂ - 5% CO₂. The superfuse flow rate was 12 ml/min. For some studies drive stimuli were delivered to the preparation through Teflon coated silver wire bipolar electrodes at a cycle length of 500 msec. This cycle length has been used in a number of other studies of digitalis effects⁸,¹¹ and permitted comparison between our present experiments and prior ones. For other studies, the preparations were allowed to beat spontaneously. For the latter type of study, two types of preparations were selected: one had relatively normal fibers that previously had been stimulated, but for which we wanted to obtain information about drug effect on spontaneous rate; the second had very abnormal fibers (as shown by the presence of markedly depressed action potentials) and was obtained from markedly dilated atria. This type of preparation was difficult and often impossible to stimulate, and hence was permitted to beat spontaneously. The methods for stimulating the preparations have been described previously.¹⁰,¹²

The tissues were impaled with 3 M KCl-filled glass capillary microelectrodes that had tip diameters <1 M and tip resistances of 15-30 Mohms. The electrodes were coupled by a 3 M KCl interface to an Ag-AgCl bar which led to an amplifier having high input impedance and input capacity neutralization. The output was displayed on a cathode ray oscilloscope (Tektronics Model 565) and photographed using Polaroid film. The tissue chamber was connected to ground through a salt bridge and an Ag-AgCl junction. The methods for calibrating the recording system and for determining the maximum rate of rise of phase 0 depolarization (V_max) have been described previously.¹⁰,¹²

After the tissues had stabilized in Tyrode's solution for 30 min, measurements were made of action potential (AP) amplitude, maximum diastolic potential (MDP), activation voltage, maximum upstroke velocity of phase 0 depolarization (V_max), action potential duration measured to 50% (APD₅₀) and 100% (APDₑ) repolarization and — in those fibers beating spontaneously — spontaneous cycle length. The methods for measuring these variables have been described previously.¹³,¹⁴

Group A

The atrial tissues were divided arbitrarily into two groups on the basis of the MDP. An MDP of -60 mV was selected as the dividing point because in previous studies of Purkinje fibers¹⁵ and in our own studies of human atria¹⁶ at maximum diastolic potentials less than -60 mV, the rapid inward current responsible for phase 0 depolarization appears to be largely inactivated and the action potential primarily is initiated by a slow inward current. To determine whether an atrium was relatively healthy or diseased, a minimum of 20 impalements were done in the first subendocardial layer of cells. Fibers having MDP > -60 mV were from relatively normal atria and are referred to as group A. Group A preparations were obtained from eight patients, four with tetralogy of Fallot, two with ventricular septal defect, one with valvular pulmonary stenosis, and one with an atrial septal defect. Two of these patients had moderately dilated atria. None had a history of atrial arrhythmias. The MDP was 72.2 ± 2.8 mV (mean ± se) and the P wave duration was 90.8 ± 1.3 msec (mean ± se).

Group B

Group B preparations were obtained from 12 patients: three with endocardial cushion defect, three with valvular pulmonary stenosis, two with transposition of the great vessels, two with tetralogy of Fallot, one with Ebstein's anomaly of the tricuspid valve, and one with single ventricle and corrected transposition of the great vessels. Ten of 12 of these patients had markedly dilated atria. Two of these ten had a history of paroxysmal atrial tachycardia, and one was in complete heart block preoperatively. The mean MDP for fibers in this group was -54.4 ± 3.3 mV and P wave duration was 114 ± 2.6 msec.

After control electrophysiologic recordings were made a single microelectrode impalement was made and maintained in each preparation. The action potential recorded here was "typical" for that preparation. The tissues then were superfused with the drug to be studied and on-line measurements were made of the effects of the drug. Three series of experiments were done.

Series I

Ouabain (Eli Lilly) was dissolved in a separate reservoir of Tyrode's solution to make a final concentration of 2 × 10⁻⁶ M. This concentration was chosen for the following reasons: First, it has been shown that ouabain, 2 × 10⁻⁶ M, in Tyrode's solution has an effect on cellular electrophysiologic properties that is compatible with a range of concentrations which may induce toxic but not fatal arrhythmias in the intact dog. To illustrate, its effect on the canine Purkinje fiber action potential is quantitatively similar to that which occurs when Purkinje fibers are superfused with blood from donor dogs that have been given a dose of ouabain (~60 µg/kg) sufficient to induce stable ventricular tachycardia or ventricular premature depolarizations.¹⁷ The second reason for using this concentration of ouabain is the following: The steady-state effect of ouabain, 2 × 10⁻⁶ M, is toxic; however, during equilibration with the tissue — and prior to attaining a steady state — it has a very different effect on the action potential. Its action is, in fact, biphasic, as was reported by Kassebaum in studies of strophanthin.⁴ Kassebaum showed that during equilibration of Purkinje fibers with strophanthin, 1.4 × 10⁻⁴ M, potassium permeability initially decreases, then increases.⁴ The biphasic effect on potassium permeability is associated with a biphasic effect on action potential characteristics. In planning the present studies we reasoned that should a similar biphasic effect of a single ouabain concentration be seen in human atria, it would permit us to study two different actions of the drug. In preliminary experiments we found that ouabain (2 × 10⁻⁶ M) does, in fact, have a
biphasic effect on atrial fibers, initially hyperpolarizing them and slowing spontaneous rate, then depolarizing them and inducing toxic rhythms. In studies of animal models, previous investigators have shown that the effects of concentrations of digitalis that reduce spontaneous rate of isolated atrial tissues are probably mediated through acetylcholine. Because it is recognized that slowing of sinus rate is a therapeutic effect of digitalis, we deemed it reasonable to call the effect of ouabain which hyperpolarized the fibers and reduced spontaneous rate “therapeutic.” That concentration which increased spontaneous rate and/or induced delayed afterdepolarizations and depolarized fibers was referred to as “toxic.” The tissues were superfused with ouabain for periods of 30 to 90 min, and the ouabain-induced changes in cellular electrophysiologic properties were observed. For the experiments on relatively healthy atria the preparations were driven at a cycle length of 500 msec and the stimulus was discontinued intermittently (for 1 min every 10 min) to permit observation of spontaneous rhythms. In experiments on diseased atria with MDP < -60 mV we utilized spontaneously firing fibers throughout.

Series 2

For these experiments we utilized spontaneously firing fibers. The tissues first were superfused with acetylcystine chloride (Sigma), 3 x 10^-4M, for 15 minutes. Within 5 to 10 min, the drug had exerted its maximum effect on the action potential and the spontaneous rhythm. The preparations then were superfused with Tyrode’s solution until control action potential characteristics and rhythm had returned. At this time, superfusion with ouabain, 2 x 10^-3M was begun, and the effects of ouabain on the transmembrane action potential and spontaneous rhythm were recorded and compared to those of acetylcholine.

Series 3

Spontaneously firing fibers were superfused with atropine sulfate (Sigma), 1 x 10^-4M for 20 min. This was the highest concentration of atropine that did not alter the spontaneous rhythm. The transmembrane action potential and rhythm then were compared to control. Then the protocol outlined in series 2 was initiated, the only difference being that atropine was included in all the superfusates.

All results reported are from microelectrode impalements of atrial fibers in the first subendocardial cell layer in which the impalement was maintained throughout the duration of the experiment. Statistical analysis of the data was performed using a paired t-test. Results are expressed as mean ± standard error.

Results

Effects of Ouabain

Table 1 shows the results of six experiments on relatively normal fibers from group A. None of these fibers developed automatic rhythms during the control period. Ouabain had a biphasic effect on AP characteristics. Approximately 15 minutes after the onset of superfusion with ouabain there were significant increases in MDP, activation voltage, AP amplitude, and Vmax. There also was a decrease in APD50 and an increase in APD100. These effects are similar to those described for mammalian atrial fibers exposed to low concentrations of digitalis,19, 20 or acetylcholine.21, 22 Following continued superfusion for approximately 60 min, there were significant decreases in MDP, activation voltage, AP amplitude, Vmax, APD50, and APD100. As will be described below, only at approximately 60 min did delayed afterdepolarizations occur. These were unassociated with spontaneous rhythm.

Table 2 shows the results of six experiments in which spontaneously firing human atrial fibers having MDP < -60 mV were superfused with ouabain. Again oua-

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<th>Table 1. Effects of Ouabain (2 x 10^-3M) on Action Potentials from Relatively Normal Human Atrial Fibers*</th>
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<td>APD100 (msec)</td>
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*Results of 6 experiments, expressed as M ± se. P (vs control) in parenthesis.
Abbreviations: AP amp = action potential amplitude; MDP = maximum diastolic potential; Vmax = maximum upstroke velocity of phase 0 depolarization; APD50, APD100 = action potential duration as measured to 50% and 100% repolarization.

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<th>Table 2. Effects of Ouabain (2 x 10^-3M) on Spontaneously Firing Fibers from Diseased Human Atria*</th>
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<td>AP amp (mV)</td>
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<td>Spont CL (sec)</td>
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*Results of 6 experiments, expressed as mean ± se. P (vs control) in parenthesis.
Abbreviations: APD50 = action potential duration; for other abbreviations see table 1.
The spontaneous firing of atrial fibers occurred in various phases of the cycle length. At 15 min, there was a significant increase in the MDP. Action potential amplitude and activation voltage also were increased, although not significantly. The spontaneous cycle length increased significantly as well. At 35 min MDP and AV had decreased and there was a marked and significant decrease in AP amplitude. This was associated with a decrease in cycle length. Compared to the healthier fibers in table 1, the diseased fibers developed toxicity significantly earlier (group A: 60 ± 10 min; group B: 35 ± 1.5 min; P < 0.001).

Figure 1 is a representative experiment showing the effect of ouabain on a normal atrial fiber (panel A). There was an initial hyperpolarization of the fiber 15 min after the onset of ouabain superfusion (panel B), followed at 60 min by marked depolarization and an increase in the slope of phase 4 depolarization (panel C).

Figure 2 shows the effects of ouabain on phase 4 depolarization in a spontaneously firing diseased atrial fiber. In panel B, after 30 min superfusion with ouabain, delayed afterdepolarizations occurred during phase 4. In panel C, the afterdepolarizations attained threshold potential resulting in a tachyarrhythmia. Delayed afterdepolarizations occurred in all 12 fibers in tables 1 and 2; for the group A fibers (table 1) approximately 60 min of ouabain superfusion were required for this toxic manifestation to occur; for the group B fibers, approximately 35 min were required. Only in group B (table 2) did the afterdepolarizations consistently reach threshold potential and initiate tachyarrhythmias.

**Comparisons of the Effects of Ouabain and AcCh**

Experiments were performed to determine, first, whether the initial effect of ouabain, hyperpolarization of fibers and slowing of spontaneous rate, was comparable to that of acetylcholine and, second — if this was the case — could it be blocked by atropine. In four experiments we compared the effects of ouabain and acetylcholine on spontaneously firing atrial fibers. Figure 3 shows the effects of AcCh and ouabain on MDP and spontaneous cycle length in these experiments. Simultaneous, significant increases in MDP and cycle length were induced by both acetylcholine and by ouabain. Figures 4 and 5 are examples of these experiments. In figure 4, superfusion with ouabain, 2 x 10^-6M, and with acetylcholine, 3 x 10^-4M, resulted in identical effects on action potential characteristics and spontaneous rate; that is, both agents induced an increase in MDP, activation voltage, and AP amplitude, along with a decrease in the slope of phase 4 depolarization and a slowing of spontaneous rate.

Figure 5 is another example of the effects of ouabain and acetylcholine in diseased atrial tissue. In this study two simultaneous impalements were made in the same atrial specimen. Although both areas were depressed, the cell depicted on the lower trace was more depressed than that on the upper. In addition ectopic activity occurred at the site recorded on the lower trace and was not propagated to the other site. Following superfusion with acetylcholine or with ouabain there were hyperpolarization, slowing of spontaneous rate, improved conduction between the two sites, and cessation of the ectopic activity.

Having demonstrated a similarity of effect of ouabain and acetylcholine, we performed four experiments in which we attempted to block this effect with atropine (table 3). The muscarinic blocker, atropine, is known to block the effects of acetylcholine on cardiac fibers. However, it has been shown that atropine blocks digitalis effects on isolated mammalian atrial fibers, we believed it important to demonstrate for this preparation whether, in fact, the hyperpolarizing and negative chronotropic effect of ouabain were the result of action at a muscarinic receptor. Spontaneously firing atrial fibers (2 from group A and 2 from group B) initially were superfused with atropine, 1 x 10^-6M, a concentration that had no effect on cycle length and resting and action potential characteristics. In the presence of atropine neither acetylcholine, 3 x 10^-4M, nor ouabain, 2 x 10^-6M,
induced significant changes in AP amplitude, activation voltage, MDP, and spontaneous cycle length. This is in marked contrast to the changes seen in the fibers that were superfused with acetylcholine or ouabain alone as in figures 3–5. Hence, prior superfusion with atropine blocked the effects of ouabain and acetylcholine on the AP and spontaneous rate. Figure 6 is one of the experiments in which we studied the effects of acetylcholine and ouabain on atropine-treated fibers.

Discussion

It should be emphasized at the outset that the relevance of these studies is solely to digitalis effects on the atrium. The actions of digitalis on the atroventricular junction, while of great importance in terms of the therapeutic and toxic effects of glycosides on the in situ heart cannot be extrapolated from these experiments. It is apparent that ouabain has a biphasic effect on the electrophysiologic properties of human atrial fibers. The initial effect, hyperpolarization associated with increases in action potential amplitude and Vmax occurs approximately 15 min after the onset of ouabain superfusion in both normal and depressed atrial fibers. These changes in the transmembrane potential characteristics could be expected to result in enhancement of conduction in the atrium as occurred in figure 4 (and in four of four experiments in which conduction was studied). In addition, in the spontaneously firing atrial fibers there was a significant decrease in automaticity associated with an increase in maximum diastolic potential and a decrease in the slope of phase 4 depolarization. These results are consistent with those seen in studies of other mammalian species.

The similar effects of acetylcholine and ouabain on spontaneous cycle length, intraatrial conduction and suppression of arrhythmias (figs. 3 and 4) are evidence supporting a parasympathomimetic action of digitalis in its antiarrhythmic effects on human atrial fibers. The atropine-induced block of the ouabain action further confirms the importance of the parasympathomimetic effect. Our results are nearly identical to those obtained by Ten Eick and Hoffman in their studies of digitalis effects on spontaneous rates of isolated rabbit atria. The decrease in rate induced by ouabain in those studies also was blocked by prior exposure to atropine. From their studies of isolated tissue the authors concluded that the effects of digitalis in slowing sinoatrial rate is secondary to a release of acetylcholine and not a direct effect. Studies by these authors and others in intact animals also have demonstrated that digitalis-induced slowing of sinoatrial rate is mediated via the parasympathetic nervous system. Hence, it is highly likely that the ouabain-induced hyperpolarization of the membrane potential in our study is due to acetylcholine release, as suggested by Ten Eick and Hoffman's study. Further evidence that isolated atrial tissues can, in fact, release acetylcholine spontaneously has been provided by Trautwein et al. That some
direct action of ouabain is exerted here, as well, cannot entirely be ruled out. However, the direct effect of the drug on atrial fibers — decreasing membrane potential and increasing phase 4 depolarization and inducing delayed afterdepolarizations — is an entirely opposite effect and hence is difficult to accept as being involved here.

These electrophysiologic effects of ouabain on human atrial fibers are consistent with the clinical antiarrhythmic effects of the drug. Specifically, the hyperpolarization and decrease in the slope of phase 4 depolarization seen in our studies would be expected to result in a slowing or suppression of ectopic atrial pacemakers. In addition, the enhancement of intraatrial conduction, also seen in some of our studies, could alter propagation through re-entrant pathways. Although we did not specifically study conduction in every preparation in which ouabain induced hyperpolarization, the association between an increase in MDP from low to normal values is known to be associated with an increased $V_{\text{max}}$ of phase 0 depolarization and an increase in conduction velocity. Hence it is reasonable to assume, based on this information and those of our experiments in which conduction was measured, that the hyperpolarization would usually be associated with enhanced conduction.

The toxic effects of ouabain on the atrial action potentials included decreases in maximum diastolic potential, activation voltage, action potential amplitude, and $V_{\text{max}},$ acceleration of repolarization, an increase in the slope of phase 4 depolarization and delayed afterdepolarizations. Delayed afterdepolarizations were seen in all 12 experiments in series 1 (tables 1 and 2) in which the fibers were allowed to develop toxicity. However only in the diseased human atria (table 2) did they consistently reach threshold potential and initiate tachyarrhythmias. In series 2 and 3 (studies with acetylcholine and atropine) the ouabain superfusion was not carried to toxicity and therefore delayed afterdepolarizations were not seen.

The delayed afterdepolarizations are comparable to those induced in canine atrial specialized fibers using acetylstrophanthidin and ventricular specialized fibers using acetylstrophanthidin or ouabain. It has been stated that the characteristics of delayed afterdepolarizations with respect to initiation and termination of arrhythmias are very similar to those described by Lown and his associates for repetitive ventricular responses. It also has been stated that afterdepolarizations probably are responsible for the occurrence of repetitive ventricular responses in the in situ heart. Whether afterdepolarizations arising in human atria as a result of digitalis toxicity are the cause of clinically occurring paroxysmal supraventricular tachycardias has not been investigated. Certainly this cellular mechanism should be considered as a possible cause of such arrhythmias.

A final, clinically important point is that ouabain superfusion of the diseased fibers (group B) resulted in toxic effects in approximately 35 min whereas 60 min elapsed

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**Table 3. Effects of Acetylcholine ($3 \times 10^{-4}M$) and Ouabain ($2 \times 10^{-5}M$) on Atropine ($1 \times 10^{-5}M$) Treated Spontaneously Firing Human Atrial Fibers**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atropine (20 min)</th>
<th>Acetylcholine (20 min)</th>
<th>Atropine (20 min)</th>
<th>Ouabain (30 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP amp (mV)</td>
<td>66.2 ± 2.8</td>
<td>66.3 ± 3.0</td>
<td>67.5 ± 1.5</td>
<td>66.4 ± 6.0</td>
<td>66.7 ± 3.6</td>
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<tr>
<td>Activation voltage (mV)</td>
<td>41.3 ± 1.3</td>
<td>40.9 ± 0.7</td>
<td>41.0 ± 0.6</td>
<td>40.5 ± 1.0</td>
<td>41.0 ± 0.7</td>
</tr>
<tr>
<td>MDP (mV)</td>
<td>61.8 ± 0.7</td>
<td>61.3 ± 1.2</td>
<td>61.6 ± 0.3</td>
<td>60.9 ± 2.6</td>
<td>61.3 ± 1.5</td>
</tr>
<tr>
<td>Spont CL (sec)</td>
<td>2.8 ± 0.4</td>
<td>2.9 ± 0.4</td>
<td>3.0 ± 0.6</td>
<td>2.9 ± 0.8</td>
<td>2.8 ± 0.5</td>
</tr>
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</table>

Results of 4 experiments, expressed as mean ± SE.
For abbreviations see tables 1 and 2.
before the development of toxicity in the relatively healthy fibers (group A). It has been a consistent clinical observation that digitalis toxicity occurs more readily in patients with severely diseased hearts than it does in patients with lesser degrees of cardiac disease. As demonstrated in tables 1 and 2, the therapeutic (parasympathomimetic) action of digitalis required the same time period in both groups of atria. That the more diseased atria developed toxicity far more rapidly offers a cellular basis for the narrowing of the therapeutic-toxic ratio that occurs clinically as cardiac disease becomes more severe. Even though the diseased fibers were firing spontaneously at a cycle length approximately 1/5 that of the rate for the normal, driven fibers, toxic changes developed more rapidly. If cycle lengths had been comparable for both groups of fibers the onset of toxicity in the diseased ones might have occurred even more rapidly. Several studies have shown that the uptake of digitalis is in part a function of the number of contractions that occur.

In our study, despite a lower number of contractions, the diseased fibers became toxic more rapidly than the healthier fibers.

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The cellular electrophysiologic effects of digitalis on human atrial fibers.
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