Effects of Cardiac Glycosides on Atrial Contractile Dysfunction After Short-term Atrial Fibrillation*

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Background: Despite a long history of use in the treatment of paroxysmal atrial fibrillation (AF), the efficacy of cardiac glycosides has not been established. If such drugs are beneficial in this condition, the general view is that the benefit must be related to their inotropic actions.

Methods and results: To assess the effects of the rapid-acting cardiac glycoside, acetylstrophanthidin (AS), on AF and AF-induced right atrial (RA) “stunning,” RA wall motion (with ultrasonic crystals), RA pressure, and peak first derivative of pressure (dp/dt) (with microtip transducers) were measured before and after 5 min of high-intensity rapid atrial stimulation (10 Hz; 10 mA; 1 ms) and after the cessation of poststimulation AF. Measurements were made in neurally intact and autonomically blockaded dogs both before and after the administration of AS (0.01 mg/kg IV bolus and 0.015 mg/kg/h IV infusion). AS prevented the post-AF reduction in RA peak dp/dt under neurally intact and autonomically blockaded conditions, and it prevented the post-AF increase in the RA end-systolic dimension and the decrease in the percentage of RA systolic shortening with autonomic blockade. AS was beneficial whether or not baseline inotropy was enhanced by AS. The duration of AF following atrial stimulation was the same before and after AS, but when compared to controls, AS treatment appeared to prolong AF.

Conclusions: Cardiac glycosides exert a favorable effect on AF-induced RA stunning, but this action is unrelated to its effects on the duration of AF. (CHEST 2000; 118:1116–1126)

Key words: atrium; cardiac glycosides; contractility; fibrillation

Abbreviations: AF = atrial fibrillation; ANOVA = analysis of variance; AS = acetylstrophanthidin; dp/dt = first derivative of pressure; LV = left ventricle, ventricular; RA = right atrium, atrial; RAEDD = right atrial end-diastolic dimension; RAESD = right atrial end-systolic dimension; RAMD = right atrial maximal dimension; RAP = right atrial pressure; SS = systolic shortening; SSI = systolic shortening index

A better understanding of atrial fibrillation (AF) has emerged from experimental investigations performed during the past several years. Studies using isochronal mapping of the atrium in experimental animals1,2 and in humans3,4 have confirmed the “circus movement” theory of AF.5 These studies have demonstrated that the arrhythmia is a manifestation of multiple, changing circuits1–4 and conditions that favor the formation of multiple disparate loops (i.e., the slowing of atrial conduction and the shortening of atrial refractoriness by reducing the wavelength of atrial impulse) foster the arrhythmia.6 Moreover, other investigations have demonstrated that AF itself creates conditions that favor the perpetuation of the arrhythmia. AF results in persistent shortening of atrial refractoriness, referred to as “electrical remodeling,”7–14 and abnormalities of atrial contractile function, so-called “stunning.”14–20 Even just a few minutes of AF can produce these changes,14,15,20 and the longer that AF lasts, the worse and more persistent the findings.7,10,14,15,17

This new information should provide a more rational approach to the therapeutics of AF. Despite a long history of use in AF, the benefits of cardiac glycosides in the treatment of this arrhythmia remain controversial.21–24 Cardiac glycosides are now used in AF mainly for ventricular rate control, an effect most evident at rest.25 This dromotropic action of cardiac glycosides is mediated primarily by their neuroexcitatory effects on the atria and atrioventricular node, actions that would also favor the persistence of AF.26 Because cardiac glycosides have inotropic effects, it would be of interest to know whether these drugs might have favorable effects on atrial stunning, and whether such effects relate to the duration of AF.
To assess the effects of cardiac glycosides on post-AF atrial stunning, a model of AF, rapid atrial electrical stimulation for 5 min, which has been shown to produce transient atrial contractile dysfunction,\textsuperscript{15,20} was used, and acetylstrophanthidin (AS), a cardiac glycoside with a time of action overlapping with the development of these abnormalities,\textsuperscript{27} was administered. Experiments were performed under neurally intact and autonomically blocked conditions, and the effects of the glycoside were determined both with baseline conditions already influenced by AS and under conditions without use of the drug. The effects of AS on the duration of AF also were determined.

**Materials and Methods**

**Preparation**

Twenty-one conditioned mongrel dogs weighing between 23 and 25 kg were anesthetized with $\alpha$-chloralose, 80 mg/kg IV, after premedication with morphine, 3 mg/kg IV. If required, supplemental $\alpha$-chloralose, in 10 mg/kg IV doses, was administered. Dogs were intubated and ventilated with a Harvard respirator, tidal volume and respiratory rate were adjusted, lungs were periodically expanded, and supplemental oxygen was administered to keep oxyhemoglobin saturation at > 90%. Ringer’s lactate (500 to 1,000 mL) supplemented with 20 mEq potassium chloride and 8 mEq magnesium sulfate were administered during preparatory surgery to mitigate the changes in hemodynamics and electrolytes. Body temperature was maintained by heating pads and was monitored by intravascular thermistors. A right lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. Intravascular sheaths were positioned in the right femoral artery, right femoral vein, and right external jugular vein; they were used for blood sampling, drug infusions, and vascular accesses for catheters. In experiments that required autonomic blockade, cervical vagi were isolated in the neck.

Pressure and length gauge traces, electrocardiograms, and epicardial electrograms, at a frequency response of 30 to 250 Hz, were displayed and recorded on a multichannel oscillograph at paper speeds of 100 to 150 mm/s. A dual-channel, custom-designed, programmable stimulator (Bloom Associates; Denver, CO) was used to deliver rectangular pulses of 1-ms duration at 10-mA strengths (oscilloscopically calibrated) through an isolation transformer.

A quadripolar catheter was attached to the right atrial (RA) appendage with two fine sutures; the distal pair was used for electrical stimulation, and the proximal pair was used to record local electrical activity. Catheters had 1-mm long electrodes with a 1-mm separation. To maintain catheter patency, 2,000 U sodium heparin were administered IV at the beginning of an experiment.

**Measurements**

**Hemodynamics:** Fluid-filled catheters were positioned in the left ventricle (LV) and RA, and pressures were measured with the manometer in the midchest taken as the zero reference. LV pressure, RA pressure (RAP), and the first derivative of these pressures (dp/dt) were obtained with catheter-tipped micromanometers (model PC-350; Millar Instruments; Houston, TX), which were calibrated in vivo using the fluid-filled catheters. Figure 1 shows a recording of these variables.

**Atrial Wall Motion:** RA diameter was measured with a pair of ultrasonic external transducers (Sonometrics Corp; London, Ontario, Canada) using a sonomicrometer (model 1001 digital sonomicrometer; Sonometrics Corp). One transducer was sutured to the atrial surface on the groove between the aorta and

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21953/)
the RA, and the other was sutured to the anterolateral wall. Figure 1 displays the RA maximal dimension (RAMD), RA end-diastolic dimension (RAEDD) (the maximal dimension just before the onset of atrial systolic shortening [SS]), and RA end-systolic dimension (RAESD) (the minimal dimension after atrial SS). Atrial SS is the difference between RAEDD and RAESD. Length measurements are expressed in millimeters. An atrial SS index (SSI) is defined as the SS percentage of RAEDD, which adjusts SS to an estimate of preload.

Protocol

Hemodynamic and atrial length measurements were made before and after 5 min of rapid atrial stimulation (10 Hz; 10 mA; 1 ms) and after the conversion of induced AF. The duration of AF was noted, and recordings were obtained at 10, 150, and 300 s postconversion. In 11 dogs, following two inductions (separated by, and the second followed by, at least a 10-min recovery period subsequent to the cessation of AF), AS (Sigma; St. Louis, MO), 0.01 mg/kg IV bolus and 0.015 mg/kg/h IV infusion, were administered and rapid atrial stimulation was repeated. After 5 min of atrial stimulation and conversion of AF, the duration of AF was noted and recordings were repeated at the same intervals as those obtained before the administration of the glycoside. Ten minutes after cessation of AF (5 min after the 300-s measurement), a baseline measurement was made (the time at which the maximal effects of AS were evident), and 5 min of rapid atrial stimulation was again initiated. After the cessation of the pacing and conversion of AF, recordings were made at the previously noted intervals. In four dogs, the controls, the same protocol of four experiments was followed, but AS was not administered.

In six dogs, the protocol was replicated exactly, but experiments were performed in the presence of autonomic blockade. β-Blockade was produced by metoprolol, 0.20 mg/kg IV bolus and 0.40 mg/kg/h IV infusion. Parasympathetic blockade was produced by bilateral cervical vagotomy and atropine, 0.05 mg/kg IV. Experiments were begun 5 to 10 min after the autonomic blockade had been produced, at a time when heart rate and BP had been found to be stable for several minutes.

Statistical Analysis

All data were entered and analyzed using computer software (SPSS/PC+; SPSS, Inc; Chicago, IL). The distribution of each variable was determined by the Kolmogorov-Smirnov test. Parametric variables were analyzed by analysis of variance (ANOVA) and the Student-Newman-Keuls test. Nonparametric variables were analyzed by the Mann-Whitney U test. Values are presented as mean ± SEM. Experiments, which had been done in pairs, were analyzed by ANOVA to ensure that findings were replicable; the average values of both experiments are presented except where otherwise noted. The null hypothesis was rejected at p = 0.05.

RESULTS

Neurally Intact Conditions

Following 5 min of atrial stimulation and an additional 102 ± 70 s of persistent AF, a brief period of RA hypercontractility ensued followed by a period of RA contractile dysfunction. The hypercontractile

![Figure 2](image-url)
state was characterized by RA peak dp/dt exceeding the baseline value. The highest RA peak dp/dt occurred in the first or second beat after the cessation of AF and averaged 2.7 ± 0.2 times the baseline value. RA peak dp/dt then gradually declined, falling below baseline after 8.9 ± 1.2 beats, or 3.8 ± 0.7 s, and reaching its nadir, generally, after 10 s. Figure 2 illustrates this bimodal contractile response following 5 min of atrial stimulation with a persistent short episode of AF. Although RAMD and RAEDD dimensions tended to increase following AF (RAESD dimensions and SS were even more variable), the changes in RA peak dp/dt (both the initial increase and subsequent decrease) occurred independently of those changes.

Table 1 and Figure 3 summarize the atrial findings, and Figure 4 provides a representative recording obtained at baseline and at 10 (lowest values), 150, and 300 s following AF. As shown, 5 min of rapid atrial stimulation producing AF resulted in a significant decrease in RA peak dp/dt, which was no longer different from baseline 2.5 min following the cessation of AF. RAP, RAMD, RAESD, SS, and SSI, were not, however, changed significantly by this perturbation. Heart rate, LV systolic pressure, LV end-diastolic pressure, and LV peak dp/dt also were not affected.

By contrast, as shown in Table 1 and Figure 3, when AS was administered, there was no decrease in RA peak dp/dt following AF. The absence of contractile dysfunction was observed both when baseline values had been obtained immediately before the administration of AS and when they were measured after this glycoside had already been administered and its maximal effects were evident. Figure 5 contrasts the effects of AF on atrial peak dp/dt when AS administration was begun 15 min before atrial stimulation was initiated with the findings in controls (experiments in which the same number of episodes of AF had preceded atrial stimulation but the cardiac glycoside was not given).

### Autonomic Blockade

Autonomic blockade reduced baseline values of RA peak dp/dt (34 ± 2.3 to 21.2 ± 0.7 mm Hg/s; \(p < 0.001\)) and LV peak dp/dt (1,535 ± 94 to 1,185 ± 64 mm Hg/s; \(p = 0.024\)) and increased baseline values of RAMD (13.9 ± 0.6 to 17.4 ± 0.8 mm; \(p < 0.001\)) and RAESD (9.8 ± 0.5 to 11.8 ± 0.4 mm; \(p = 0.005\)). Despite these changes, the contractile response to 5 min of atrial stimulation and an additional 3 ± 1 s of persistent AF was similar to that observed under neurally intact conditions: a brief period of RA hypercontractility followed by one of RA contractile dysfunction, albeit affecting more variables. After the cessation of AF, RA peak dp/dt was initially 2.8 ± 0.4 times the baseline value, but gradually declined, falling below baseline after 10.3 ± 1.8 beats, or 4.3 ± 0.5 s, and reaching its nadir, generally, after 10 s.

Table 2 and Figure 6 summarize the atrial findings at baseline and at 10, 150, and 300 s after AF. Even though baseline values of variables reflecting RA function were already depressed when compared to the neurally intact values, RA peak dp/dt (ANOVA, \(p < 0.013\)) and SSI (\(p < 0.042\)) decreased and RAESD (\(p < 0.015\)) increased following AF. RAP, RAMD, SS, heart rate, LV peak dp/dt, LVS, and LVED, however, did not change.

As shown in Table 2 and Figure 6, in contrast to the findings without the glycoside, when AS was

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### Table 1—RA Dimensions and Function in Neurally Intact Dogs*

<table>
<thead>
<tr>
<th>Variables</th>
<th>RAA, mm Hg</th>
<th>RA dp/dt, mm Hg/s</th>
<th>RAMD, mm</th>
<th>RAESD, mm</th>
<th>SS, mm</th>
<th>SSI, %</th>
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<tbody>
<tr>
<td>Before glycoside (n = 11)</td>
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</tr>
<tr>
<td>Baseline</td>
<td>4.5 ± 0.2</td>
<td>34.0 ± 2.3</td>
<td>13.9 ± 0.6</td>
<td>9.8 ± 0.5</td>
<td>3.4 ± 0.4</td>
<td>25.4 ± 2.1</td>
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<td>10 s</td>
<td>4.6 ± 0.1</td>
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<td>10.5 ± 0.6</td>
<td>3.5 ± 0.4</td>
<td>24.8 ± 2.2</td>
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<td>150 s</td>
<td>4.7 ± 0.2</td>
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<td>300 s</td>
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<td>30.3 ± 2.0</td>
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<td>3.3 ± 0.2</td>
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<tr>
<td>Baseline</td>
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<td>35.1 ± 3.8</td>
<td>13.3 ± 0.5</td>
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<td>Control (n = 4)</td>
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<tr>
<td>Baseline</td>
<td>4.3 ± 0.7</td>
<td>31.5 ± 5.8</td>
<td>14.5 ± 0.5</td>
<td>10.9 ± 0.6</td>
<td>3.0 ± 0.3</td>
<td>21.9 ± 2.1</td>
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<td>10 s</td>
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<td>14.9 ± 0.5</td>
<td>2.7 ± 0.4</td>
<td>18.5 ± 2.7</td>
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<td>150 s</td>
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<td>14.7 ± 0.6</td>
<td>11.6 ± 0.8</td>
<td>2.5 ± 0.2</td>
<td>18.0 ± 1.9</td>
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<tr>
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<td>4.0 ± 0.5</td>
<td>27.9 ± 4.0</td>
<td>14.4 ± 0.5</td>
<td>11.1 ± 0.6</td>
<td>2.8 ± 0.2</td>
<td>20.4 ± 1.4</td>
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</table>

*Values given as mean ± SEM. RAA = RA A-wave pressure.
†p < 0.05 vs baseline value.
administered, there was no decrease in RA peak dp/dt following AF. Moreover, AS attenuated the increase in RAESD and the decrease in SSI, so that the changes following AF were no longer significant. The benefits of AS were evident whether or not baseline values had been augmented by the glycoside (ANOVA p > 0.4 for RA peak dp/dt and SSI comparing the response to AF with baseline obtained without glycoside vs with baseline demonstrating maximal effect of glycoside).

AF

As shown in Figure 7, the duration of AF induced at baseline was not different from that after the administration of AS. Autonomic blockade sharply reduced the duration of AF; there was, however, no additional change after the administration AS (Fig 7). Although the baseline duration (first two measurements) of AF in control dogs was the same as that found in the neurally intact dogs before the administration of the glycoside (102 ± 70 vs 106 ± 72 s), AF duration in the control dogs at a time comparable to that at which the glycoside had been administered was sharply lower (106 ± 72 vs 7 ± 3 s; p = 0.12 [Mann-Whitney U test]). Thus, the lack of a difference in AF duration following AS might actually indicate an enhancement of the arrhythmia by the glycoside.

**Discussion**

**Main Results**

The present study demonstrates that the cardiac glycoside AS attenuates the atrial contractile dysfunction, the so-called stunning, that follows short-term AF. This favorable action of AS was observed in neurally intact and autonomically blockaded conditions, and it was found both when baseline atrial function was determined before the administration of the cardiac glycoside and when baseline function had been maximally enhanced by the drug. This effect of AS on atrial contractile function, however, was not associated with any favorable influence on AF itself; in fact, the findings suggest that the cardiac glycoside may actually promote AF even as it exerts a beneficial effect on atrial contractile function.

**Experimental Model**

The model of AF that was used is similar to that of Leistad et al. However, in addition to species differences (dogs vs pigs), there were other dissimilarities: higher intensity, albeit fewer, electrical stimuli were used to induce AF in our study. This was done to ensure that AF would be elicited with each experiment. However, higher intensity stimuli produce a greater release of neurohormones that promote AF. With repeated stimulations, the duration
of AF tended to shorten, probably related to progressively less electrorelease of these hormones. The neural actions of AS appeared to offset this effect. Although the general findings of the models were similar, a brief hypercontractile period followed by one of reversible hypocontractility, the effects on various variables differed. We failed to observe a significant decrease in atrial SS with AF under neurally intact conditions, a paramount finding in the swine model, but we did find that this occurred with autonomic blockade. The difference was probably caused by a more intense sympathetic response in our study related to the use of α-chloralose, an anesthetic that tends to maintain autonomic effects, and the preservation of atrioventricular conduction, which permitted greater systemic effects of AF.

**Theoretical Considerations**

AF is characterized by multiple changing reentrant circuits. The arrhythmia is triggered by atrial extrasystoles and atrial tachycardias and is sustained by a milieu of shortened and heterogeneous atrial refractoriness. AF creates conditions that serve to perpetuate itself, so-called electrical remodeling. The fast and irregular stimulations of AF produce marked and disparate decreases in atrial refractoriness, the latter enhanced by the inherent differences of the refractory periods at various atrial sites. As our study and others have demonstrated, AF also produces contractile abnormalities, so-called stunning. The longer that AF lasts, the longer the changes produced by the arrhythmia will persist. As we have found in the anesthetized dog and as Daoud et al have observed in humans, following several minutes of AF, the hypocontractility that ensues resolves after a few minutes of sinus rhythm. Similarly, the shortening of atrial refractory periods that follows the cessation of AF or tachycardia lasting 10 min resolves also after only a few minutes. By contrast, following the cessation of AF that has been sustained by continuous rapid atrial pacing or following cardioversion of chronic AF in humans, the electrical remodeling and stunning of the atrium may take many days or even weeks to be reversed.

The changes in excitation and contraction that are produced by AF have been related to alterations at the cellular and molecular levels. AF has been shown to produce a shortening of the duration of the atrial action potential and a depression of the atrial
myocyte function. These changes have been related to a reduction of L-type calcium current and to reduced calcium systolic transients. By contrast, the L-type calcium channel blocker verapamil also has been found to attenuate post-AF electrical remodeling and stunning.

In this context, the actions of AS in AF, and perhaps cardiac glycosides in general, can be examined. The acute neuroexcitatory action of AS, particularly its vagal effects, would explain a lack of benefit of the drug on paroxysmal AF. The vagus nerve shortens atrial refractoriness, increases the heterogeneity of atrial refractory periods, and sustains AF. Previously, we have found a lack of benefit of AS on the duration of AF induced by short bursts of rapid atrial stimulation. Those investigations also demonstrated a prolongation of AF at toxic dosages of AS, effects that can be explained by the intense neurohumoral actions including sympathetic effects, and by the delayed afterdepolarizations (oscillations) that occur with excessive amounts of cardiac glycosides.

Because atrial hypocontractility following AF is associated with reduced calcium transients, the direct cellular action of cardiac glycosides, which increases cytosolic calcium, could explain the favorable action of AS on atrial stunning. The post-AF abnormalities of atrial excitation and contractility, however, have been attributed to calcium overload engendered by frequent depolarizations. This expla-

### Table 2—RA Dimensions and Function in Neurally Blockaded Dogs

<table>
<thead>
<tr>
<th>Variables</th>
<th>RAA, mm Hg</th>
<th>RA dp/dt, mm Hg/s</th>
<th>RAMD, mm</th>
<th>RAESD, mm</th>
<th>SS, mm</th>
<th>SSI, %</th>
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<tr>
<td>Baseline</td>
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<td>17.4 ± 0.8</td>
<td>11.8 ± 0.4</td>
<td>4.4 ± 0.6</td>
<td>25.2 ± 1.9</td>
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<tr>
<td>10 s</td>
<td>4.9 ± 0.3</td>
<td>14.6 ± 2.2†</td>
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<td>150 s</td>
<td>4.7 ± 0.3</td>
<td>17.4 ± 1.1</td>
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<td>12.2 ± 0.5†</td>
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<td>28.6 ± 2.1</td>
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<tr>
<td>300 s</td>
<td>4.8 ± 0.3</td>
<td>18.7 ± 1.0</td>
<td>17.5 ± 0.7</td>
<td>11.7 ± 0.4</td>
<td>4.7 ± 0.6</td>
<td>28.1 ± 2.2</td>
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<td>Glycoside (n = 6)</td>
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<tr>
<td>Baseline</td>
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<td>10 s</td>
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<td>28.9 ± 1.8</td>
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*Values given as mean ± SD. See Table 1 for abbreviations not in text.
†p < 0.05 vs baseline values.
‡p < 0.05 vs 10-s value.
nation is based, at least in part, on the observation that verapamil antagonizes these changes. In addition to its direct actions on L-type calcium channels, IV verapamil also increases plasma catecholamines. Although the attenuation of post-AF electrical remodeling by verapamil has been observed in both neurally intact and autonomically blocked conditions, the beneficial effects of verapamil on post-AF contractile dysfunction have been reported either without blockade or with severe atrial contractile dysfunction. Thus, the actions of verapamil on atrial stunning may be related, at least in part, to the sympathomimetic effects evoked by the drug. Nevertheless, even if the detrimental effects of AF are due to calcium overloading, AS might still improve the contractile function of the stunned atrium in a fashion analogous to the effects of epinephrine and postextrasystolic potentiation on ischemic reperfusion injury, a condition also believed to be caused by calcium overload.

Recent investigations may provide insights into the "calcium paradox" of AF-induced atrial stunning and into how cardiac glycosides might exert favorable effects on this phenomenon. An increased frequency of depolarizations produces an enhanced entry of calcium into the cytosol, causing more calcium to be released by the sarcoplasm reticulum, increased calcium transients, and more forceful contractions. Concomitantly, increased cytosolic calcium inhibits the inward L-type calcium channel. Following 1 min of rapid atrial stimulation, only hypercontractility is evident, as the contractile force gradually dissipates with the cessation of stimulation but never falls significantly below baseline. With 5 to 15 min of stimulation, the effects of increased cytosolic calcium will exert a favorable effect on contractile proteins yet still will inhibit calcium entry by way of the L-type calcium channel, producing a brief period of hypercontractility that is followed by one of hypocontractility. After longer periods of stimulation, a new steady state might be reached in which cytosolic calcium may even be normal because of a substantial inhibition of calcium entry through the L-type calcium channel. However, when stimulation is stopped, there would be less calcium entry, at least transiently, resulting in the attenuation of calcium release by the sarcoplasmic reticulum and reduced calcium transients, with only atrial hypocontractility evident. Because the enhanced entry of calcium by cardiac glycosides is not dependent on the L-type calcium channel (but is dependent on sodium-potassium adenosine triphosphatase inhibition and on the reverse sodium-calcium exchanger), these drugs may ensure that adequate calcium is available to the contractile proteins, even though the L-type calcium channel has been inhibited. AS has, in fact, been found to have a favorable effect on the atrial interval-strength relationship, its actions being more intense when atrial inotropy is depressed.

Figure 6. RA peak dp/dt (mean ± SEM) at baseline and at 10, 150, and 300 s after the cessation of AF, before the administration of AS (○) (n = 6), and after the administration of AS (●) (n = 6) in dogs with autonomic blockade. The decrease in RA peak dp/dt at 10 s after AF is shown to occur in dogs before the administration of AS but not after the administration of the glycoside (comparison by ANOVA). * = significance of the change from baseline with no glycoside (p < 0.05, Student-Newman-Keuls test).
blood flow\textsuperscript{48} and energetics,\textsuperscript{49} which might contribute to atrial stunning but are not likely to be favorably influenced by cardiac glycosides.

**Cardiac Glycosides in Paroxysmal AF**

The findings in our study are consistent with previously reported clinical investigations that have assessed the effects of cardiac glycosides on paroxysmal AF.\textsuperscript{20–24} The view that cardiac glycosides might be beneficial in the treatment of this condition has been based largely on uncontrolled observations, suggesting a high frequency of cardioversion following administration of IV digoxin.\textsuperscript{50} The administration of cardiac glycosides given for congestive heart failure also is believed to result in an increased conversion rate of AF to sinus rhythm.\textsuperscript{51} Randomized controlled studies, however, have demonstrated little benefit of these drugs for alleviation AF.\textsuperscript{21,22,24} When compared to controls, neither IV\textsuperscript{22} nor oral\textsuperscript{21} cardiac glycosides have been found to increase the number of cardioversions or to shorten the time it takes for the cessation of AF. Moreover, on 24-h ambulatory ECG recordings of patients being monitored for\textsuperscript{24} or having demonstrated\textsuperscript{22} AF, those patients receiving digoxin had a comparable number of episodes of paroxysmal AF,\textsuperscript{23,24} albeit more prolonged attacks,\textsuperscript{23} than those not receiving the drug. By contrast, in a randomized, double-blind, placebo-controlled, crossover designed study in which episodes of AF were reported with an event recorder during periods of treatment with digoxin, the interval between episodes of AF lengthened and the average ventricular rate of those events was 15 beats/min slower.\textsuperscript{24} Thus, the administration of IV or oral cardiac glycosides does not appear to be effective in converting or shortening episodes of AF.\textsuperscript{21,22} Findings that are consistent with the effects of AS on experimental AF observed in this study. When AF occurs in patients receiving digoxin, the duration of AF or the ventricular rate at onset also does not appear be improved.\textsuperscript{23,24} However, in such patients the average ventricular rate of AF may be slowed (as a dromotropic effect of cardiac glycosides\textsuperscript{26}) and the interval between episodes of AF may be lengthened (perhaps in some way related to its antistunning actions).\textsuperscript{24}

**Limitations and Clinical Implications**

The relevance of the findings of this study to clinical AF in humans must consider the acute conditions of the model, species differences, and the manner of induction of AF, in contrast to spontaneous AF, as possible limitations. Also, adaptive changes to more prolonged AF and to cardiac glycosides administered over longer periods also might influence the findings. Our study does not address the possible beneficial effects of cardiac glycosides in reducing the triggers of AF, atrial extrasystoles and tachycardias, and it does not examine the benefits of cardiac glycosides on congestive heart failure that
might prevent AF by reducing atrial size and improving neurohumoral conditions. However, to the extent that cardiac glycosides attenuate atrial stunning following the conversion of AF to sinus rhythm, they would enhance ventricular performance by improving atrial “booster” actions and possibly also would reduce the risk of stroke attributable to stunning. Nevertheless, only clinical investigations can determine whether the benefits of cardiac glycosides suggested by our study have importance in humans at risk for paroxysmal AF.

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