VENTRICULAR RATE CONTROL IN CHRONIC ATRIAL FIBRILLATION DURING DAILY ACTIVITY AND PROGRAMMED EXERCISE: A CROSSOVER OPEN-LABEL STUDY OF FIVE DRUG REGIMENS

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OBJECTIVES
We compared the effects of five pharmacologic regimens on the circadian rhythm and exercise-induced changes of ventricular rate (VR) in patients with chronic atrial fibrillation (CAF).

BACKGROUND
Systematic comparison of standardized drug regimens on 24-h VR control in CAF have not been reported.

METHODS
In 12 patients (11 male, 69 ± 6 yr) with CAF, the effects on VR by 5 standardized daily regimens: 1) 0.25 mg digoxin, 2) 240 mg diltiazem-CD, 3) 50 mg atenolol, 4) 0.25 mg digoxin + 240 mg diltiazem-CD, and 5) 0.25 mg digoxin + 50 mg atenolol; were studied after 2 week treatment assigned in random order. The VR data were analyzed by ANOVA with repeated measures. The circadian phase differences were evaluated by cosinor analysis.

RESULTS
The 24-h mean (±SD) values of VR (bpm) were: digoxin: 78.9 ± 16.3, diltiazem: 80.0 ± 15.5, atenolol: 75.9 ± 11.7, digoxin + diltiazem: 67.3 ± 14.1 and digoxin + atenolol: 65.0 ± 9.4. Circadian patterns were significant in each treatment group (p < 0.001). The VR on digoxin + atenolol was significantly lower than that on digoxin (p < 0.0001), diltiazem (p < 0.0002) and atenolol (p < 0.001). The time of peak VR on Holter was significantly delayed with regimens 3 and 5 which included atenolol (p < 0.03). During exercise, digoxin and digoxin + atenolol treatments resulted in the highest and lowest mean VR respectively. The exercise Time-VR plots of all groups were nearly parallel (p = ns). The exercise duration was similar in all treatment groups (p = ns).

CONCLUSIONS
This study indicates that digoxin and diltiazem, as single agents at the doses tested, are least effective for controlling ventricular rate in atrial fibrillation during daily activity. Digoxin + atenolol produced the most effective rate control reflecting a synergistic effect on the AV node. The data provides a basis for testing the effects of chronic suppression of diurnal fluctuations of VR on left atrial and ventricular function in CAF. (J Am Coll Cardiol 1999; 33:304–10) © 1999 by the American College of Cardiology

Atrial fibrillation has recently emerged as the most common cardiac arrhythmia in clinical practice (1). It is now recognized as being responsible for significant morbidity and increased mortality (2). It has been known that with the onset of atrial fibrillation the mean ventricular rate over 24 h is substantially higher than that during sinus rhythm in the same patient during atrial fibrillation. Such an increase in heart rate may lead to a complex of adverse reactions including palpitations, dizziness, lassitude, shortness of breath and symptoms of heart failure in patients with significant heart disease (3). Sustained increases in ventricular rate (VR) during atrial fibrillation lead to decrease in left ventricular ejection fraction (LVEF) to a variable degree (4). To this must be added the significant incidence of thromboembolic stroke (5). There is evidence suggesting that the overall complex of adverse reactions can be reduced by restoration and maintenance of sinus rhythm (6) or VR control by AV conduction blocking drugs combined with anticoagulants (7). However, the relative superiority of these two approaches in the treatment of atrial fibrillation is uncertain, but it is the subject of several major ongoing clinical trials.

Therefore, control of the ventricular response combined with anticoagulation remains one of the two primary goals...
in the treatment of chronic atrial fibrillation (CAF) that is widely used in clinical practice. Historically, digitalis has been the pharmacologic agent of choice in control of ventricular response in atrial fibrillation (8). However, it has been suggested that in a fairly large group of patients the heart rate during exercise and even during normal daily activity cannot be adequately controlled with digitalis alone (9–13). Other agents including beta-adrenergic blocking agents and rate-lowering calcium-channel blockers alone and in combination with digoxin have been investigated and found to be more effective in reducing ventricular response in these patients (9–11,14–21). Beta-blockers are effective in reducing the VR in CAF at rest and during exercise (22). Verapamil and diltiazem, two calcium-channel blockers with potent negative dromotropic properties, have been studied extensively in CAF, and have been found to produce strikingly similar effects on VR control (18). When combined with digoxin, these agents commonly produce VR reductions that are more pronounced at rest and during exercise (18,20,21,23,24). However, the rate control over 24 h by the standard drug regimens has not been systematically investigated (25). The purpose of this study was to compare the effects of 5 standard drug regimens consisting of digoxin, diltiazem, atenolol, digoxin + diltiazem and digoxin + atenolol on the mean 24-h heart rates, circadian patterns of ventricular responses and on programmed exercise in the same group of patients with CAF.

METHODS

Study patients. Twelve patients (11 men and 1 woman, mean age 69 ± 6 yr, range 57 to 78 yr) took part in the study. All had documented CAF, resistant to attempted cardioversion, of at least one year duration. All patients were carefully evaluated by history, physical examination, ECG, chest X-ray and echocardiography. Seven of the 12 had lone atrial fibrillation and five had one or more underlying cardiovascular disorders, including hypertension (n = 5), surgically corrected mitral stenosis (n = 1) and ischemic heart disease (n = 2). Three of the 12 did not receive beta-blocker therapy due to chronic obstructive pulmonary disease. All patients were in New York Heart Association functional class I or II. All antiarrhythmic drugs were discontinued before the start of the study. Before this study, the subjects were on digoxin for ventricular rate control.

Two patients received additional calcium channel blocker therapy with either verapamil or diltiazem.

Exclusion criteria. The patients with echocardiographic LVEF less than 35%, heart rate less than 55 bpm, Wolf-Parkinson-White syndrome, clinically significant renal, thyroid or hepatic dysfunction, uncontrolled hypertension, sick sinus syndrome, implanted pacemaker, unstable angina or acute myocardial infarction or persistent systolic blood pressure less than 95 mm Hg were excluded from the study. Patients receiving other medications such as theophylline, clonidine or inhaled beta-agonists, which might affect ventricular response in AF, as well as those with previous exposure to amiodarone, were excluded. Subjects who recently used an investigational drug or those with a history of untoward reaction to any of the medications used in the present study were also excluded.

All patients gave informed consent before participation in the study. The protocol was approved by the Human Investigations Committee at this institution.

Study design. In a crossover, open-label outpatient study, the following five treatment regimens were investigated: 1) digoxin 0.25 mg/day, 2) diltiazem-CD 240 mg/day, 3) atenolol 50 mg/day, 4) digoxin 0.25 mg/day plus diltiazem-CD 240 mg/day and 5) digoxin 0.25 mg/day plus atenolol 50 mg/day. These doses were selected for fixed drug regimens as being those that had been reported to be effective and best tolerated in the largest numbers of patients with atrial fibrillation. For example, Roth et al. (23) reported excessive side effects with 360 mg/day of diltiazem-CD. Lanas et al. (26) reported that in patients with CAF, 100 mg/day atenolol was associated with deterioration of NYHA functional class, whereas 0.25 mg/day of digoxin was well tolerated. All medications were administered once daily. The patients received each of the drug regimens in a random sequence. Each regimen was administered for two weeks, ensuring that steady-state drug concentrations were attained and provided for an adequate period of washout of the previous treatment regimen. Following the two-week period on each regimen, a 24-h Holter recording was obtained and the mean VR during each hour were calculated. All Holter tapes were analyzed on a Del Mar StrataScan 563 scanner (Del Mar Avionics, Irvine, California) by a single experienced biotechnician. The Holters were repeated if there were less than 21 h of artifact-free recording. All the tapes included in the analysis yielded an hourly mean VR for each of the 24 h without missing values.

On the following morning, a symptom-limited progressive-load treadmill exercise test was performed using the modified Naughton protocol (6). Patients were instructed to abstain from food and coffee for at least 4 h before testing. A standard 12-lead ECG and blood pressure were obtained at rest and throughout the exercise test and recovery period. Following the completion of the treadmill study, patients were started on the next randomly assigned
Figure 1. Circadian distribution of hourly mean VR in patients with CAF as influenced by various treatment regimens (Dig + dlt = digoxin + diltiazem; Dig + atn = digoxin + atenolol). The “hour of the day” refers to a 24 h clock with hour 0 being midnight. All regimens exhibited significant circadian variation of VR (p < 0.001). Digoxin and diltiazem given alone had similar overall rates during the 24 h. Compared with digoxin, atenolol alone and digoxin + atenolol markedly attenuated the circadian rhythmicity. Note that beta-blockade tended to shift the peak ventricular rate to a later time in the afternoon and the combination of digoxin and atenolol was the most effective regimen in reducing the ventricular rate in atrial fibrillation. See text for details.

Table 1. Comparisons of Mean Ventricular Rates (VR) Measured over 24 Hours, During Daytime (6 am to 6 pm), and During Nighttime (6 pm to 6 am)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>24 Hour VR mean ± SD (n)</th>
<th>Daytime VR mean ± SD</th>
<th>Nighttime VR mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digoxin</td>
<td>78.9 ± 16.3 (10)</td>
<td>84.7 ± 19.6</td>
<td>72.8 ± 13.5</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>80.0 ± 15.5 (12)</td>
<td>83.8 ± 18.4</td>
<td>76.3 ± 13.2</td>
</tr>
<tr>
<td>Atenolol</td>
<td>75.9 ± 11.7 (8)</td>
<td>77.0 ± 14.6</td>
<td>74.8 ± 9.9</td>
</tr>
<tr>
<td>Digoxin + diltiazem</td>
<td>67.3 ± 14.1* (12)</td>
<td>71.8 ± 17.4‡</td>
<td>62.9 ± 11.2</td>
</tr>
<tr>
<td>Digoxin + atenolol</td>
<td>65.0 ± 9.4† (9)</td>
<td>64.7 ± 10.3§</td>
<td>65.4 ± 9.2¶</td>
</tr>
</tbody>
</table>

*This value is lower than those with digoxin (p < 0.004), diltiazem (p < 0.0005) and atenolol (p < 0.007) treatments. †This value is lower than those with digoxin (p < 0.0001), diltiazem (p < 0.0002) and atenolol (p < 0.001) treatments. ‡This value is lower than those with digoxin (p < 0.02) and diltiazem (p < 0.007) treatments. ¶This value is lower than those with digoxin (p < 0.0001), diltiazem (p < 0.0001) and atenolol (p < 0.0002). ††This value is lower than those with diltiazem (p < 0.002) and atenolol (p < 0.007).
treated group exhibited minimum differences between day and night (Table 1). The circadian patterns of VR of patients on digoxin, diltiazem and digoxin treatments were substantially parallel and were significantly different from those on atenolol and digoxin (p < 0.001).

Cosinor analysis of circadian variation. In the atenolol- and digoxin + atenolol-treated groups, the midday peak was markedly attenuated with the development of a smaller peak later in the evening. The 24-h VR data of each subject were fitted to a cosine curve through nonlinear regression analysis. The hourly mean VR data and the corresponding cosine curves of 4 cases representing typical, best, borderline accepted and rejected fits are presented. The time of peak ventricular rate from midnight was calculated from the estimated phase of the cosine fit. See Table 2 and the text for details.

Ventricular rate changes during exercise. The mean VR changes for each treatment group during 12 min of exercise are presented in Figure 3. For the purpose of statistical analysis, the VR changes during the first 5 min were chosen because 50 out of 53 attempted exercise tests contained complete data for this duration. According to ANOVA with repeated measures, the exercise curves (time vs. VR plots) showed a significant linear trend (p < 0.0001) and were substantially parallel with nonsignificant differences in slopes (p = ns). When all the groups were analyzed together, the effect of treatment was

![Figure 2](image_url1)

Figure 2. Cosinor modeling of the circadian pattern of VR in patients with CAF for comparison of the effects of different treatments on the phase of the circadian patterns. The 24-h VR data of each subject were fitted to a cosine curve through a nonlinear regression analysis. The hourly mean VR data and the corresponding cosine curves of 4 cases representing typical, best, borderline accepted and rejected fits are presented. The time of peak ventricular rate from midnight was calculated from the estimated phase of the cosine fit. See Table 2 and the text for details.

![Figure 3](image_url2)

Figure 3. Effect of various pharmacologic regimens on exercise-induced VR in patients with CAF. There was a linear trend in increases in VR on all 5 regimens. The mean VR on digoxin + atenolol treatment was the lowest and was significantly lower than those on digoxin, diltiazem and digoxin + diltiazem. See text for details.

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Phase Angle of Cosine Fit (Radians)</th>
<th>Time of Peak Ventricular Rate (hour)</th>
<th>Number Included</th>
<th>Number Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Digoxin</td>
<td>3.7 ± 0.5</td>
<td>13.6 ± 1.8</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>2. Diltiazem</td>
<td>4.0 ± 0.5</td>
<td>14.5 ± 2.4</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>3. Atenolol</td>
<td>4.8 ± 0.7*</td>
<td>17.5 ± 2.6*</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>4. Digoxin + diltiazem</td>
<td>3.5 ± 0.8</td>
<td>12.6 ± 2.8</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>5. Digoxin + atenolol</td>
<td>5.1 ± 1.2*</td>
<td>18.5 ± 4.5*</td>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

*Significantly more delayed than digoxin-, diltiazem- and dig + diltiazem-treated groups (p < 0.03). The time of peak ventricular rate was significantly delayed (p < 0.03) when atenolol was included in the treatment (Groups 3 and 5).
significant (p < 0.0001) which is reflected in the vertical separation of the exercise curves in Figure 3. The treatment effect was not significantly different at different VR during exercise (p = ns), even when both linear and nonlinear components in the exercise curves were considered together. The digoxin-treated group had the highest mean VR (125 ± 28 beats per minute [bpm]), which was significantly higher than that of diltiazem (105 ± 15 bpm, p < 0.02), atenolol (93 ± 26 bpm, p < 0.005), digoxin + diltiazem (102 ± 29 bpm, p < 0.03) and digoxin + atenolol (82 ± 9 bpm, p < 0.0001) treatment groups. The VR on digoxin + atenolol treatment was the lowest and was significantly lower than those on digoxin (p < 0.0001), diltiazem (p < 0.0001) and digoxin + diltiazem (p < 0.01). It was lower than VR on atenolol with borderline significance (p = 0.077).

The mean exercise parameters of subjects who exercised for at least 5 min are presented in Table 3. The peak exercise VR for the atenolol- and digoxin + atenolol-treated groups were lower than those of the other groups and were significantly lower than that in the digoxin treated group (p < 0.01). The mean exercise durations were similar in all treatment groups (p = ns). The peak systolic blood pressure of the atenolol treated group was the lowest and was significantly lower than those for all other groups except for that on the digoxin + atenolol-treated group (p < 0.05). The peak diastolic blood pressures followed a similar trend without statistical significance.

**DISCUSSION**

Although many studies have compared two or three medical regimens for the control of VR in atrial fibrillation, to our knowledge, direct comparisons of such multiple regimens using the same cohort of patients in a crossover design have not been reported. Furthermore, VR control in CAF, as a function of the time of the day, has not been compared among different drug regimens. In the current study, it was our goal to compare the precise degree of control of ventricular responses achieved during daily activities and controlled exercise on five regimens in common clinical use. The only agent in common use that was excluded was verapamil; its effects are virtually identical to those of diltiazem at rest and during exercise (18) while it interacts pharmacokinetically with digoxin (29).

**Circadian rhythmicity of ventricular rate control.** The results revealed that the circadian pattern of VR changes seen in CAF treated with digoxin was maintained at a somewhat equal level with calcium-channel antagonism with diltiazem. In contrast, atenolol lowered the rate predominantly during the daytime, being less effective when beta-adrenergic stimulation was low as during sleep (30). Furthermore, the beta-blocker markedly attenuated VR without abolishing its circadian pattern. The most effective regimen for attenuating increases in the VR over the entire 24 h as well as during exercise was the combination of beta-blockade and digoxin, a regimen which is known to induce a marked reduction in adrenergic activity with an augmentation in vagal activity. Our data indicated that the effects of atenolol and digoxin on modulating the VR in atrial fibrillation was synergistic both during daily activities over 24 h as well as during treadmill exercise. For example, linear increases in ventricular response on all five regimens during treadmill exercise were found but, again, the combination of digoxin and atenolol was the most effective regimen in attenuating the VR during exercise. Thus, the overall findings of this study have much clinical significance insofar as they allow a rational basis for the choice of individual drugs as well as combination regimens for VR control in CAF over the diurnal cycle as well as physical activity. It should be emphasized that beta-blockade may reduce exercise capacity (22), whereas calcium-channel blockers such as verapamil or diltiazem may increase it while controlling the ventricular response (31) in atrial fibrillation. No such differences were found in our study which, in contrast to previous reports, used exercise protocol that did not produce maximal stress. However, different doses of drugs may result in differences in exercise parameters.

**Changing role of digoxin in ventricular rate control.** Digoxin as a single regimen, although still being the most widely used as first-line therapy for VR control in atrial fibrillation, proved less effective in this study, both during
ordinary daily activities as well as during treadmill exercise. However, its effects over 24 h were similar to that of a moderate dose of diltiazem-CD given alone. Nevertheless, during exercise, diltiazem, a calcium channel-blocker which exhibits a significant degree of noncompetitive adrenergic antagonism, significantly attenuated the exercise-induced increases in VR against the background of digoxin therapy which acts largely by its vagomimetic action on the AV node. The combination of the inhibitory effects of digoxin and diltiazem on the AV node seemed to be synergistic particularly during exercise, particularly in the pattern of control of VR over 24 h. The combination regimen provided a significantly greater VR control than individual agents, as previously reported (23). Higher doses (e.g., 360 mg/day) of diltiazem than that used in this study (240 mg-CD) have been found to markedly increase side effects without significant improvement in VR control (23).

The effect of digoxin plus beta-blockade for ventricular rate control. The most striking finding in the current study was the effect of the combined action of atenolol and digoxin during exercise as well as over the 24 h noted on Holter recordings. The mean VR over the 24 h was lower on digoxin + atenolol than those on all other regimens studied reflecting the synergistic effect on the AV node of the vagomimetic actions of the cardiac glycoside and of the beta-blocking actions of atenolol. It is likely that a similar or even a greater effectiveness on VR control might have resulted from higher dose of the beta-blocker alone. However, it is known that higher doses of beta-blockers are associated with a greater incidence of adverse reactions and possibly diminished exercise capacity (26). On the other hand, the shift of the peak ventricular response from about a mean of 13 h to 18 h during the 24-h period in the case of atenolol suggests that this beta-blocker might be best administered twice daily rather than once daily when used for the purposes of rate control in atrial fibrillation. Thus, the overall effects of a longer-acting beta-blocker such as nadolol or timolol on the pattern of the circadian rhythmicity of VR control in atrial fibrillation might differ.

Potential significance of adequate ventricular rate control in atrial fibrillation. In recent years, a number of lines of evidence have suggested that sustained elevated heart rate due to cardiac arrhythmias may lead to tachycardia-induced cardiomyopathy that may be reversible (4). For example, incessant supraventricular tachycardia has the potential to induce striking but reversible reductions in LVEF in patients without cardiac disease (32). Similarly, uncontrolled ventricular response in patients with atrial flutter and fibrillation may induce heart failure which resolves either with AV nodal ablation and ventricular pacing at slower rate (33) or simply by control of the ventricular response in atrial fibrillation by rate-lowering drugs. For example, Grogan et al. (4) have shown that congestive heart failure with markedly depressed LVEF can follow in the wake of uncontrolled VR in atrial fibrillation. In their cases, there was a marked and relatively rapid improvement in heart failure, LVEF and exercise capacity when VR was slowed by AV nodal blocking drugs. Thus, an adequate rate control may not only relieve symptoms in atrial fibrillation but it may confer other benefits.

The results of the current study draw attention to a number of clinically significant issues. For example, what might constitute an “adequate” VR control in all patients with atrial fibrillation remains undefined (25). It is not known whether indices of adequate control should now include patterns of change in the circadian rhythmicity of VR, mean heart rate from 24-h Holter recordings or a defined reduction in the peak heart rate during a standardized exercise test. The results of this study show that combined regimens of pharmacologic agents can be developed to test the possibility that continuous and sustained control of VR over 24 h might lead to the correspondingly sustained improvement in ventricular function and exercise capacity along with relief of symptoms.

Study limitations. This study was neither blinded nor placebo-controlled. Because our intention was not to demonstrate the ability of various drugs to control VR but rather to compare differences in action and efficacy, the nonblinded approach may not be a serious limitation. Although the number of patients studied was relatively small, using the same cohort of patients for drug regimen comparisons provided statistical validity for the study. However, no strong conclusions can be drawn regarding the potency of different regimens used in this study on exercise capacity. Further studies of a blinded nature may be of value in determining the precise effects on exercise capacity relative to the degree of control of ventricular response in patients with atrial fibrillation. However, the fact that the data obtained revealed significant and consistent changes with respect to other major parameters such as the degrees of control of the ventricular response during exercise as well as during daily activities attests to the validity and clinical relevance of the data from this open-label study.

Conclusions. Digoxin continues to be the first-line therapy for the control of VR in most patients with CAF, but the data presented here indicate that, of all the regimens tested in the same cohort of patients, it was one of the least effective agents both during ordinary daily activities and during treadmill exercise. During exercise, diltiazem, a calcium channel-blocker with noncompetitive antiadrenergic property, significantly attenuated the exercise-induced increases in VR against the background of digoxin therapy. The combination of the inhibitory effects of digoxin and diltiazem on the AV node seemed to be synergistic, but the regimen was significantly less potent than a similar combination regimen of atenolol and digoxin. The mean VR over the 24 h was lower on digoxin + atenolol than those on digoxin, diltiazem or digoxin + diltiazem, reflecting the markedly synergistic effect on the AV node of the vagomimetic actions of the cardiac glycoside and of the beta-blocking actions of atenolol. The data provide a rational
basis for the choice of a pharmacologic regimen for rate control in atrial fibrillation and an approach for defining the significance of various regimens for preventing the deterioration of ventricular and left atrial function.

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REFERENCES