Efficacy of Oral Diltiazem to Control Ventricular Response in Chronic Atrial Fibrillation at Rest and During Exercise

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Although digoxin is often the first choice for control of ventricular response in chronic atrial fibrillation, it fails to slow exercise rates. Diltiazem, a calcium channel antagonist that slows atrioventricular conduction, was administered to 16 patients who failed to achieve adequate rate control on low level exercise testing despite digoxin therapy. Therapeutic response to diltiazem was assessed with submaximal and maximal exercise tests and 24 hour ambulatory electrocardiographic monitoring.

During the diltiazem treatment phase, ventricular response at rest diminished (96 ± 17 versus 69 ± 10 beats/min, \( p < 0.001 \)) as did rate during submaximal exercise (155 ± 28 versus 116 ± 26, \( p < 0.001 \)), maximal exercise (163 ± 14 versus 133 ± 26, \( p < 0.001 \)) and average ventricular response during 24 hour monitoring (87 ± 13 versus 69 ± 10, \( p < 0.001 \)). Rate at rest decreased 26 ± 15% and submaximal exercise rate diminished 24 ± 12%. Thirteen (81%) of the 16 patients exhibited at least 15% slowing of rate at rest and during submaximal exercise. Eleven patients (69%) reported alleviation of symptoms. There was no change in serum digoxin levels during diltiazem treatment (1.3 ± 0.5 versus 1.3 ± 0.6 ng/ml, \( p = \text{NS} \)). On withdrawal of diltiazem, ventricular response returned to baseline values.

Diltiazem is an effective agent for control of ventricular response, both at rest and during exercise, in digoxin-treated patients with chronic atrial fibrillation. 

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Control of the ventricular response is the primary goal in the treatment of chronic atrial fibrillation. Traditionally, digitalis glycosides have been the pharmacologic agents of first choice to modulate ventricular response in this setting. Though digoxin often can control heart rate at rest, it affords little, if any, protection against rapid rates during exercise (1-10). Beta-adrenergic blocking agents may be useful supplements to digoxin therapy (2,8,9); however, they have several important contraindications and actually may diminish exercise capacity (2,10).

Conduction through the atroventricular (AV) node is mediated by the calcium-dependent slow channel. Calcium channel antagonists prolong AV node conduction and refractoriness (11-14), and have proved useful in the treatment of supraventricular tachycardias that utilize the AV node. In multiple studies, verapamil has been shown to terminate AV node reentrant tachycardia (15,16) as well as decrease both the rest and exercise ventricular response in atrial fibrillation (1,4-7,17). Diltiazem has electrophysiologic properties similar to those of verapamil (11,14,18,19) and has been documented to prevent the induction of AV node reentry (20-22).

It was our goal to determine the value of diltiazem to impede AV conduction in patients with chronic atrial fibrillation. Thus, control of ventricular response was assessed at rest, during controlled exercise and during daily activities.

Methods

Study patients (Table 1). Nineteen patients with chronic atrial fibrillation were enrolled in the study and 16 completed the entire study protocol. Eleven were men and five were women. The mean age was 66 ± 12 years (range 38 to 79). The study entry criterion required a ventricular response rate greater than 100 beats/min at the completion of a limited standardized exercise test (3 minutes, 3 miles/h, 0° grade). Digoxin was continued if it had previously been part of the
Table 1. Clinical Characteristics of 16 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr) &amp; Sex</th>
<th>CV Diagnosis</th>
<th>Digoxin Dose (mg/day)</th>
<th>Other CV Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79M CAD, HTN</td>
<td></td>
<td>—</td>
<td>Diuretic, nitrate</td>
</tr>
<tr>
<td>2</td>
<td>75M LAF</td>
<td></td>
<td>0.125</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>56M LAF</td>
<td></td>
<td>0.25</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>58M LAF</td>
<td></td>
<td>0.5</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>74M LAF</td>
<td></td>
<td>0.25</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>73M CAD, HTN</td>
<td></td>
<td>0.125</td>
<td>Nitrate</td>
</tr>
<tr>
<td>7</td>
<td>76F LAF</td>
<td></td>
<td>0.25</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>75F HTN</td>
<td></td>
<td>0.25</td>
<td>Diuretic, prazosin</td>
</tr>
<tr>
<td>9</td>
<td>50M MVR</td>
<td></td>
<td>0.25</td>
<td>Diuretic, warfarin</td>
</tr>
<tr>
<td>10</td>
<td>70M DM, HTN</td>
<td></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>11</td>
<td>77M LAF</td>
<td></td>
<td>0.25</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>58F MVR, HTN</td>
<td></td>
<td>0.25</td>
<td>Diuretic, warfarin, prazosin</td>
</tr>
<tr>
<td>13</td>
<td>59M CM, CHF</td>
<td></td>
<td>0.25</td>
<td>Nitrate, diuretic, captopril, warfarin</td>
</tr>
<tr>
<td>14</td>
<td>58F MS</td>
<td></td>
<td>0.25/0.375*</td>
<td>Diuretic, nitrate, warfarin</td>
</tr>
<tr>
<td>15</td>
<td>72M CAD, CHF</td>
<td></td>
<td>—</td>
<td>Diuretic</td>
</tr>
<tr>
<td>16</td>
<td>38M MS</td>
<td></td>
<td>0.25</td>
<td>Diuretic, warfarin</td>
</tr>
</tbody>
</table>

*Alternate day dosages. AF = lone atrial fibrillation; CAD = coronary artery disease; CHF = congestive heart failure; CM = idiopathic cardiomyopathy; CV = cardiovascular; DM = diabetes mellitus; HTN = hypertension; MS = mitral stenosis; MVR = mitral valve replacement.

patient's medical regimen. For those taking digoxin, the digoxin dose was adjusted to maintain a serum level in the therapeutic range (0.5 to 2.0 ng/ml) before entry into the formal study. Once this dosage was determined, digoxin was continued throughout the study without adjustment. All but three patients were on long-term digoxin therapy. All other antiarrhythmic medications including beta-adrenergic blockers, calcium channel blockers and class 1 antiarrhythmic agents were discontinued at least five half-lives before the start of the formal study.

Exclusion criteria were recent use of an investigational drug, unstable angina or acute myocardial infarction, Wolff-Parkinson-White syndrome, clinically significant renal or hepatic failure, sick sinus syndrome without a functioning pacemaker, uncontrolled hypertension, systolic blood pressure less than 95 mm Hg, cardiac or other diseases that prevented upright exercise, or a history of untoward reaction to diltiazem. A history of congestive heart failure was not a contraindication to participation.

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

Study design. The study was divided into three open label phases (Fig. 1). The initial phase served as a baseline period to allow recording of baseline variables after the digoxin dose had been adjusted. The second phase involved the administration of diltiazem (Cardizem) and observation of its effect on specific variables. In the final phase diltiazem was withdrawn to provide a comparison period and to account for the effects of training (23). Phases occurred as 3 consecutive 1 week periods.

During the baseline pretreatment phase 1, a history and physical examination were performed followed by a 12 lead electrocardiogram, submaximal exercise treadmill test (3 minutes, 3 miles/h, 0° grade) and 24 hour ambulatory monitoring (Cardiodata MK3 system with analysis at George Washington University). Heart rate at rest was measured with the patient supine. Ventricular response and blood pressure were monitored at 1 minute intervals during and for 3 minutes after exercise testing. Ventricular response was counted over at least 20 seconds at 1 minute intervals.

![Figure 1](image-url) Study design. + = optional high dose phase if the 3 minute submaximal exercise heart rate was still greater than 135 beats/min. DIL = diltiazem; ECG = electrocardiogram; ETT = exercise treadmill test.
The patient then entered phase 2 and was treated with diltiazem, 60 mg four times daily. After 7 days a repeat examination including a 3 minute submaximal exercise test and 24 hour monitoring was performed. If peak exercise ventricular response was still greater than 135 beats/min, the diltiazem dose was increased to 90 mg four times daily and repeat testing was performed after an additional week of study. At the completion of phase 2 on maximal dose diltiazem therapy (60 or 90 mg four times daily) all patients underwent a symptom-limited (maximal) exercise test using a Bruce or modified Bruce protocol. This followed the 3 minute exercise test by a 15 minute rest period.

Patients entered phase 3 after testing on treatment with the optimal diltiazem dose. Diltiazem was discontinued for 7 days whereon a complete examination was performed, including submaximal (3 minute) and maximal exercise tests and 24 hour ambulatory monitor.

Digoxin serum levels were determined immediately before exercise at each visit and diltiazem levels by high pressure liquid chromatography at visits during phase 2. All exercise tests were performed 2 to 5 hours after the diltiazem dose was administered when diltiazem levels would be expected to achieve their peak concentration (18). Careful observation for and documentation of adverse effects were made.

Analysis of data. Results are presented as mean ± SD. Statistical analysis was performed using the Student’s t test for paired and unpaired data.

Results

Nineteen patients met the criteria for entry into the study, but the study was terminated prematurely in three of them: one withdrew voluntarily without explanation and two developed intolerable side effects within 3 days of diltiazem therapy. The remaining 16 patients constituted the diltiazem study group listed in Table I. Results during active treatment (phase 2) are reported for the optimal (maximal) diltiazem dose: 60 mg four times daily in 11 patients and 90 mg four times daily in 4 patients; 1 patient was studied at 30 mg four times daily because of adverse effects at a greater dose (see later).

Control of ventricular response. Therapy with diltiazem resulted in significant reductions in various rest and exercise variables (Table 2, Fig. 2). Ventricular response was reduced at rest, at all levels of submaximal exercise and at conclusion of the maximal exercise evaluation. Rest ventricular rate dropped 26 ± 15% and 3 minute submaximal exercise ventricular rate diminished 24 ± 12%. Thir-

Table 2. Comparative Data Before and During Diltiazem Therapy in 16 Patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Diltiazem</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular response (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At rest</td>
<td>96 ± 17</td>
<td>69 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 Minute ex (submaximal ETT)</td>
<td>145 ± 25</td>
<td>104 ± 21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 Minutes ex (submaximal ETT)</td>
<td>152 ± 26</td>
<td>110 ± 22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3 Minutes ex (submaximal ETT)</td>
<td>155 ± 28</td>
<td>116 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak ex (maximal ETT)</td>
<td>163 ± 14</td>
<td>133 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average 24 hour</td>
<td>87 ± 13</td>
<td>69 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Maximal 24 hour</td>
<td>184 ± 24</td>
<td>148 ± 26</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Minimal 24 hour</td>
<td>51 ± 7</td>
<td>41 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>sBP, rest</td>
<td>136 ± 30</td>
<td>131 ± 21</td>
<td>NS</td>
</tr>
<tr>
<td>dBP, rest</td>
<td>83 ± 14</td>
<td>72 ± 20</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>sBP, 3 Minutes ex (submaximal ETT)</td>
<td>160 ± 35</td>
<td>148 ± 26</td>
<td>NS</td>
</tr>
<tr>
<td>dBP, 3 Minutes ex (submaximal ETT)</td>
<td>80 ± 14</td>
<td>79 ± 9</td>
<td>NS</td>
</tr>
<tr>
<td>RPP, 3 Minutes ex (submaximal ETT)</td>
<td>25,433 ± 9,015</td>
<td>17,431 ± 5,318</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP = blood pressure (mm Hg); dBP = diastolic blood pressure; ETT = exercise treadmill test; RPP = rate-pressure product; sBP = systolic blood pressure.
electrocardiographic monitoring before and during the diltiazem treatment period. Results are the average 24 hour rate and the maximal and minimal rates recorded during the monitoring period. Data presented as mean values ± SD. BPM = beats per minute.

Figure 3. Ventricular response recorded with 24 hour ambulatory electrocardiographic monitoring before and during the diltiazem treatment period. Results are the average 24 hour rate and the maximal and minimal rates recorded during the monitoring period. Data presented as mean values ± SD. BPM = beats per minute.

Figure 4. Comparison of "slow" (pretreatment rate ≤ 90 beats/min at rest) (dashed line) and "fast" (pretreatment rate > 90 beats/min at rest) (solid line) subgroups before and during diltiazem therapy. Data are presented as mean values ± SD. BPM = beats per minute.

heart rate-systolic pressure product at maximal levels of exertion decreased significantly during diltiazem therapy, primarily because of a blunted rate response.

Maintenance serum diltiazem levels. The mean serum diltiazem level at maximal dosage was 234 ± 187 ng/ml. Diltiazem level correlated only with the percent change in heart rate at rest (r = 0.55, p < 0.05).

Diltiazem interaction with digoxin. The serum level of digoxin in the 13 patients receiving digoxin before the start of therapy was 1.3 ± 0.5 ng/ml. During diltiazem therapy, the level was 1.3 ± 0.6 ng/ml (p = NS).

Symptomatic response. Eleven (69%) of the 16 patients in the study group had subjective alleviation of symptoms of fatigue, palpitation and breathlessness during the diltiazem treatment period. Four patients showed no improvement and one patient had slight worsening of symptoms.

Adverse effects. Two patients developed severe dizziness necessitating diltiazem discontinuation before exercise evaluation on treatment. Two patients developed an erythematous rash; however, medication could be continued to study completion. One patient experienced mild dizziness shortly after diltiazem administration and one described nausea only if diltiazem was not taken with meals. One study subject had mild transient edema. Another patient developed nausea, headache and edema while receiving diltiazem, 60 mg four times daily, and symptoms completely resolved when the dose was reduced to 30 mg four times daily. Four of the eight patients were older than 70 years or receiving 360 mg of diltiazem daily.

The one patient with preexistent congestive heart failure and chronic ventricular ectopic rhythm manifested sustained (40 seconds) ventricular tachycardia at a rate of 130/min during the second minute of the submaximal exercise test while receiving diltiazem, 60/mg. The episode was asymptomatic, without observed hemodynamic changes and was
self-terminating. Exercise before diltiazem during treatment with digoxin alone had revealed no ventricular tachycardia; however, baseline 24 hour Holter monitoring demonstrated frequent and complex ventricular ectopic activity. After discontinuation of diltiazem and institution of specific antiarrhythmic therapy, repeat exercise studies revealed no ventricular tachycardia. No change in ventricular ectopic activity during diltiazem was noted in the other 15 patients.

There were no episodes of symptomatic bradycardia or regularization of rhythm during the period of diltiazem therapy. Hypotension did not occur in any patient and there were no episodes of orthostatic hypotension.

Discussion

Limitation of digoxin therapy. Digoxin therapy for rate control in atrial fibrillation is well entrenched in the tradition of cardiovascular medicine. Whereas digoxin has modest success in reducing rest ventricular response in atrial fibrillation, it has failed to prevent excessive tachycardia during exertion (1-10). Our study clearly confirms these observations. In the baseline phase, submaximal exercise quickly produced ventricular rates above 150 beats/min despite therapeutic digoxin levels. Others (5,8) have demonstrated that increasing digoxin doses to achieve levels in the upper therapeutic range also fails to significantly blunt exercise tachycardia. The explanation for these findings resides in digoxin’s mechanism of action in chronic atrial fibrillation. Rate control by digoxin is primarily effected by cholinergic potentiation. During stress or exercise, parasympathetic activity is overwhelmed by sympathetic discharges, thus negating digoxin’s minimal autonomic effects.

Effects of beta-adrenergic blockade. Given the sympathetic effects on AV node function, it is logical to assume that beta-adrenergic blockade would be useful and, indeed, rest and exercise rate control has been achieved with this class of drugs (2,8,9). Beta-blockers, however, are limited by their well known side effects and often result in reduced exercise capacity despite rate slowing. In one study (2) of nadolol in atrial fibrillation, 65% of the patients had a significant decrement in exercise time on beta-blocker therapy. A small group of propranolol-treated patients showed either no improvement or worsening of exercise tolerance (10).

Calcium channel blockade as alternative therapy. Depolarization of AV node tissue is a calcium-dependent process by way of the slow channel. Calcium channel blockade with verapamil depresses AV node action potential amplitude and lengthens nodal refractoriness (14,24). The effects of verapamil on the electrical properties of the AV node are independent of autonomic influences (24,25) and continue to modulate AV conduction during exercise (26). Oral verapamil therapy for chronic atrial fibrillation augments rate control in digitalized patients (1,4,6,7), and can be satisfactory as monotherapy without concomitant digoxin (5). Mean ventricular rate by 24 hour electrocardiographic monitoring is slowed (7,17) and exercise rates are significantly reduced (1,4-7).

While oral verapamil exhibits efficacy in atrial fibrillation, definite limitations to its widespread use exist (27) including its negative inotropic properties (28,29), elevation of serum digoxin levels (30-32), delayed drug accumulation (33) and emergence of accelerated junctional rhythm (34,35).

Efficacy of diltiazem for rate control in atrial fibrillation. Diltiazem shares with verapamil a potent negative dromotropic effect without significant negative inotropic effects (36-39). Mitchell et al. (40) found that diltiazem prolonged the atrial-His interval by 12% in sinus rhythm and by 22% in constant paced rhythm. Nodal functional refractory period lengthened 6%, nodal effective refractory period 16% and Wenckebach cycle length 13% in the same study (40). Others (11,14,18,19) have found similar AV node conduction delay and prolongation of refractoriness. These electrophysiologic properties, similar to but less potent than those of verapamil, make diltiazem potentially useful in the treatment of supraventricular tachycardias. Intravenous diltiazem was effective in the short-term management of paroxysmal supraventricular tachycardia (AV node reentry with and without retrograde conduction in an accessory pathway) (20,21). Oral diltiazem successfully prevented induction of paroxysmal supraventricular tachycardia and during the follow-up period maintained prophylaxis in a group of patients with recurrent arrhythmia (22).

Given this background, diltiazem would be expected to reduce ventricular response in patients with atrial fibrillation. Thiesen et al. (41) noted a significant reduction in mean ventricular rates after the short-term administration of oral diltiazem and during oral maintenance therapy. Recently, Roth et al. (42) found a significant improvement in rest and exercise rate control when diltiazem was added to digoxin in 12 patients with primarily rheumatic heart disease and atrial fibrillation. Diltiazem therapy alone, particularly at high doses, produced adequate rate reduction as well. In 3 weeks of follow-up, the digoxin-diltiazem combination also achieved significant rate reduction. Our study confirms and expands these preliminary findings with diltiazem. Diltiazem-treated patients had moderate slowing of rest ventricular response, and rates were sharply blunted at all stages of submaximal exercise and at the peak of maximal exercise. These results are consistent with diltiazem’s direct effect on AV conduction.

Ambulatory electrocardiographic monitoring provides a less artificial method for documenting drug efficacy. Diltiazem was capable of maintaining a slower average rate in the 24 hour period. The limits (maximal and minimal) of ventricular rate similarly changed during therapy.

We could not document an overall improvement in maximal exercise time in our study group as a whole. This failure to improve exercise capacity may be due to the ad-
Diltiazem is an effective agent for heart rate control in patients with chronic atrial fibrillation treated with concomitant digoxin. Symptoms improved and results were confirmed at rest, during various levels of exertion and during 24 hour ambulatory monitoring. Diltiazem therapy had no effect on digoxin levels and was not associated with serious adverse effects.

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References

18. Smith MS, Vergheze CP, Shand DG, Pritchett ELC. Pharmacokinetic...


