Effects of long-term treatment with amiodarone on exercise hemodynamics and left ventricular relaxation in patients with hypertrophic cardiomyopathy

WALTER J. PAULUS, M.D., PH.D., PAUL NELLENS, M.D., GUY R. HEYNDRICKX, M.D., PH.D., AND ERIC ANDRIES, M.D.

ABSTRACT  The influence of long-term treatment with amiodarone on exercise hemodynamics and on left ventricular relaxation was studied prospectively in patients with hypertrophic cardiomyopathy. Rest-exercise hemodynamics (n = 9) and echocardiographic relaxation indexes (isovolumic relaxation time, dPW/dt) (n = 11) were measured in control conditions and after 5 weeks of oral amiodarone treatment (600 mg daily first week, 400 mg daily second week, 200 mg daily afterwards). Long-term amiodarone treatment in patients at rest caused a significant drop in heart rate from 80 ± 11 to 75 ± 11 beats/min (p < .05), a rise in mean pulmonary artery pressure from 19 ± 7 to 25 ± 10 mm Hg (p < .02), and a rise in mean pulmonary capillary wedge pressure from 11 ± 4 to 17 ± 8 mm Hg (p < .05). Systemic arterial pressure, cardiac output, and systemic vascular resistance remained unaltered. Exercise tolerance assessed by serial supine bicycle stress testing was reduced in six of nine patients. Amiodarone treatment caused a significant rise in pulmonary capillary wedge pressure from 22 ± 8 to 37 ± 9 mm Hg (p < .001) at the highest identical workloads and from 26 ± 10 to 37 ± 9 (p < .005) at maximal symptom-limited workloads. Similarly, mean pulmonary artery pressure rose from 37 ± 15 to 51 ± 18 mm Hg (p < .01) at highest identical workloads and from 42 ± 19 to 51 ± 18 mm Hg (p < .01) at maximal symptom-limited workloads. There were no significant differences at maximal exercise level in heart rate, systemic arterial pressure, cardiac output, or exercise factor. Echocardiographic studies performed before and during long-term amiodarone treatment revealed no change in isovolumic relaxation time, end-diastolic or end-systolic posterior wall thickness, and peak posterior wall thinning rate. A negative inotropic action of amiodarone could explain the worsened rest and exercise hemodynamics observed during long-term treatment of patients with hypertrophic cardiomyopathy. Echocardiographic relaxation indexes remained unaltered despite the elevated left ventricular filling pressures. This finding could suggest a deleterious effect of amiodarone on myocardial inactivation, possibly similar in mechanism to the depressed myocardial inactivation observed in hypothyroidism.


β-ADRENERGIC blocking agents, calcium channel-blocking agents, and disopyramide have been variably successful for the relief of symptoms in patients with hypertrophic cardiomyopathy. β-Blockade was associated with amelioration of dyspnea or angina but failed to alter the primary cardiomyopathic process.

Moreover, the response to therapy was not uniform and the effects on left ventricular relaxation and diastole remained controversial. In recent years the results obtained with calcium channel-blocking drugs have been encouraging. Salutary effects have been reported on the primary myopathic process, symptoms and exercise tolerance, left ventricular outflow tract obstruction, left ventricular relaxation, and diastole. The beneficial effect of calcium channel-blocking drugs needs to be individually assessed because of adverse effects such as high-degree atrioventricular block or worsening of heart failure and outflow tract obstruction. Disopyramide was used because of its...
negative inotropic action,\textsuperscript{18} which decreased outflow tract gradients, thereby reducing symptoms in some patients but not in all of them.\textsuperscript{3}

The benzofuran derivative amiodarone was successfully used for the treatment of ventricular tachycardias,\textsuperscript{19} and the drug has been proposed to improve survival in patients with hypertrophic cardiomyopathy suffering from high-grade ventricular arrhythmia when compared with conventional antiarrhythmic agents.\textsuperscript{20} Moreover, long-term amiodarone treatment was recently reported to improve cardiac symptoms\textsuperscript{21} and to increase exercise capacity in patients with hypertrophic cardiomyopathy.\textsuperscript{22} These effects were accompanied by an improvement of rapid left ventricular filling on radionuclide left ventricular angiograms.\textsuperscript{23} The hemodynamic effects of long-term amiodarone therapy as well as its influence on left ventricular echocardiographic relaxation indexes have not yet been reported in patients with hypertrophic cardiomyopathy. We therefore undertook a prospective study to investigate the influence of long-term amiodarone treatment on rest and exercise hemodynamics as well as on echocardiographic left ventricular relaxation indexes in patients with hypertrophic cardiomyopathy.

**Methods**

**Patients.** Eleven patients (four women, seven men) (ages 39 to 81 years, mean 57) with clinical, echocardiographic, or angiographic evidence of hypertrophic cardiomyopathy were studied prospectively. Hypertrophic cardiomyopathy was defined by the presence of a hypertrophied nondilated left ventricle in the absence of a cardiac or systemic disease that itself could produce left ventricular hypertrophy.\textsuperscript{24} Informed consent was obtained for each patient. Before and during long-term amiodarone treatment, nine patients (four women, five men) underwent both hemodynamic studies and echocardiographic investigations, whereas two patients underwent only sequential echocardiographic studies. Patient characteristics, predominant symptoms, functional class (NYHA), distribution of left ventricular hypertrophy, and presence and severity of systolic anterior motion (SAM) are summarized in table 1. At the time of the control study, three patients were in functional class I (NYHA), six patients were in class II, and two patients were in class III. Based on echocardiographic or angiographic findings, the distribution of left ventricular hypertrophy was classified as septal, apical, or concentric.\textsuperscript{3, 25, 26} Patients with septal left ventricular hypertrophy (patients 3, 4, 6, 8, 9, and 11) belonged to type III

**TABLE 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Symptoms, functional class (NYHA)</th>
<th>Distribution of LVH\textsuperscript{A}</th>
<th>Presence and severity of SAM\textsuperscript{B}</th>
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<tr>
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<td>C Am</td>
<td>C</td>
<td>Am</td>
</tr>
<tr>
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<td>64</td>
<td>F</td>
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<td>Apical</td>
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<tr>
<td>2</td>
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<td>M</td>
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<td>Concentric</td>
<td>No SAM</td>
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<td>3</td>
<td>39</td>
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<td>Angina, dyspnea</td>
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<td>Severe SAM</td>
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<td>70</td>
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<td>Septal (type III)</td>
<td>Severe SAM</td>
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C = control; Am = during amiodarone treatment; LVH = left ventricular hypertrophy.

\textsuperscript{A}Apical, concentric, septal (type III): anterior + posterior interventricular septum + anterolateral wall involvement.

\textsuperscript{B}Mild = minimal distance left-side interventricular septum to anterior mitral leaflet > 10 mm; severe = SAM septal contact quantified by an index value expressed as the ratio of the duration of SAM septal contact divided by the time from the onset of SAM to onset of SAM septal contact.
TABLE 2
Hemodynamic data at rest

<table>
<thead>
<tr>
<th>Patient</th>
<th>Heart rate (beats/min)</th>
<th>RAP (mm Hg)</th>
<th>PAP (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>SAP (mm Hg)</th>
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<td>4</td>
<td>11</td>
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<td>93</td>
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<td>7</td>
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<td>80 ± 11</td>
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<td>4 ± 1</td>
<td>8 ± 3</td>
<td>19 ± 7</td>
<td>25 ± 10</td>
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</table>

RAP = mean right atrial pressure; PAP = pulmonary artery pressure, expressed as systolic/diastolic, mean; PCW = pulmonary capillary wedge pressure expressed as a-wave, v-wave, mean; SAP = systemic arterial pressure expressed as systolic/diastolic, mean; SVR = systemic vascular resistance; C = control; Am = during amiodarone treatment.

involvement of the entire ventricular septum and extension into the anterolateral left ventricular free wall.27 Two patients with septal left ventricular hypertrophy (patients 7 and 10) could not be subclassified because of a lack of two-dimensional echocardiographic studies. Systolic anterior motion (SAM) of the mitral valve was present in five patients (Nos. 3, 4, 6, 8, and 11). SAM was graded as mild (minimal distance of the left side of the interventricular septum to the anterior mitral leaflet exceeding 10 mm), moderate (minimal distance of the left side of the interventricular septum to the anterior mitral leaflet smaller than 10 mm), or severe.28 For patients with severe SAM (patients 3, 6, and 11) an index value of SAM was calculated before and during long-term amiodarone treatment (table 1). This index value equals the ratio of the duration of SAM septal contact divided by the time from the onset of SAM to the onset of SAM septal contact.29 Before the control study, three patients with SAM on the echocardiogram underwent left heart cardiac catheterization, which confirmed the presence of an intraventricular pressure gradient (patient 3, 90 mm Hg; patient 11, 40 mm Hg; patient 8, inducible gradient > 30 mm Hg). Selective coronary arteriography was performed before the control study in patients with angina (patients 1, 3, 8, and 11) and revealed no significant coronary artery stenoses (coronary artery luminal diameter narrowing < 50%). Patients with abnormal thyroid function tests, detectable thyroid antibodies, or restrictive lung disease were excluded from the study. On a 24 hr electrocardiographic monitoring performed less than 1 month before the control study, all patients were in sinus rhythm with no or low grade ventricular arrhythmias. The absence of supraventricular arrhythmias or high-grade ventricular arrhythmias avoids the confounding influence of improved arrhythmia control on hemodynamic and echocardiographic measurements during long-term amiodarone treatment. All medications were stopped 48 hr before the control hemodynamic and/or echocardiographic study and all other medications were withheld during the period of the oral amiodarone drug regimen, except in one patient, whose antiepileptic drugs were continued throughout. After the control investigations, all patients were started on oral amiodarone (600 mg daily during the first week, 400 mg daily during the second week, and 200 mg daily afterwards as a maintenance dose). Repeat hemodynamic and echocardiographic studies were performed after 5 weeks of oral amiodarone treatment. At the time of the second study there was a significant prolongation of the corrected QT interval from 442 ± 37 to 494 ± 23 msec (n = 11; p < .05), which is consistent with the myocardium being impregnated by amiodarone as a result of the long-term drug regimen.30 Despite the low dose of amiodarone during maintenance treatment and the short observation period, most patients developed a photosensitive rash. There was no toxic effect on thyroid function, no pulmonary fibrosis, and no drug-induced hepatitis. After the repeat hemodynamic or echocardiographic study, the drug was discontinued in all patients.

Hemodynamic studies. Right heart cardiac catheterizations were performed by brachial vein cutdown or by the percutaneous jugular vein approach. A thermodilution balloon-tipped catheter was advanced into the pulmonary artery and a small Teflon catheter was introduced in the brachial or radial artery for continuous systemic arterial pressure monitoring. Systemic arterial pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, and right atrial pressure were measured by HP 1290A transducers, which were referenced to atmosphere at the midstch level. The pressure signals and the three bipolar standard leads of the electrocardiogram were recorded on a Gould ES 1000 multichannel recorder. At rest, hemodynamic recordings of right atrial, pulmonary capillary wedge, pulmonary arterial, and systemic arterial pressures were obtained. During exercise, pulmonary capillary wedge, pulmonary arterial, and systemic arterial pressures were recorded at 1 min intervals. Cardiac output measurements at rest or in the last minute of exercise were performed by the thermodilution technique (Edwards Laboratories, 9520 A Cardiac Output Computer; average of at least three values) or by the Fick principle (oxygen content of expired air continuously measured by Oxylab oximeter).31 At rest and at maximal exercise, level pulmonary artery and arterial blood samples were obtained and oxygen saturations were determined with an OSM2 Hemoximeter (Radiometer Copenhagen). All patients underwent supine bicycle exercise stress testing on a Monark ergometer with stepwise (3 min interval) increment (12.5 W) of workload while pedaling at a fixed pace of 50 rounds/min. Initial workloads and the exercise protocol were identical in both exercise tests. The exercise factor (table 3) was calculated as the ratio of the exercise-induced increment of cardiac output to the increment of oxygen consumption (normal value 6.0).32 Pressure signals were digi-
TABLE 2
(Continued)

<table>
<thead>
<tr>
<th>Cardiac output (l/min)</th>
<th>SVR (dyne-sec-cm⁻¹)</th>
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<td></td>
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</tr>
<tr>
<td>5.3</td>
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<td>8.9</td>
<td>9.4</td>
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<tr>
<td>5.9 ± 1.4</td>
<td>6.2 ± 1.9</td>
</tr>
</tbody>
</table>

NS

Echocardiographic studies. M mode echocardiograms of the mitral valve and the left ventricular cavity were recorded with an Irex System II multiple-channel recorder or derived by M mode cursor from a short-axis view of the mitral valve and the left ventricular cavity recorded by a sector scanner (Irex Meridian). The mitral valve echocardiogram, left ventricular cavity echocardiogram, phonoecardiogram of aortic valve closure sound (A₂), and single-lead electrocardiogram were recorded at a paper speed of 100 mm/sec in control conditions and after 5 weeks of long-term amiodarone administration (figure 3). The left ventricular isovolumic relaxation time (IVRT) (table 4, figure 3) was calculated as the interval (msec) between the first high-frequency components of the aortic valve closure sound (vertical line at A₂ in figure 3) and the opening point of the mitral valve leaflets on the mitral valve echocardiogram. Posterior wall endocardium and epicardium of the left ventricular cavity echocardiogram were digitized every 5 msec from the peak of the R wave of the electrocardiogram to the peak of the R wave of the subsequent beat and were analyzed with an Apple M 0001 WP 512K computer. A sixth-order polynomial was fitted to the diastolic portion of the posterior wall thickness data for determination of the first derivative to calculate peak posterior wall thinning rate (dpW/dt, mm/sec) (table 4). The interobserver, intraobserver, day-to-day, and cycle-to-cycle variability coefficients for IVRT and dpW/dt determined by this computer-assisted analysis were found to be 5% or less.13,33

Statistical analysis. All data are reported (tables 2, 3, and 4) as mean ± SD. Statistical significance was set at p < .05 and was determined by t test of correlated samples.

Results

Hemodynamic data: rest. Hemodynamic variables were recorded under control conditions and after 5 weeks of oral amiodarone treatment (table 2). During long-term amiodarone treatment there was a drop in resting heart rate from 80 ± 11 to 75 ± 11 beats/min (p < .05) and a rise in mean right atrial pressure (RAP), mean pulmonary artery pressure (PAP), and mean pulmonary capillary wedge pressure (PCW), respectively, from 4 ± 1 to 8 ± 3 mm Hg (p < .001), 19 ± 7 to 25 ± 10 mm Hg (p < .02), and 11 ± 4 to 17 ± 8 mm Hg (p < .05). Mean systemic arterial pressure, cardiac output, and systemic vascular resistance remained unaltered. Individual changes in resting mean PCW during long-term amiodarone treatment are shown in figure 1, middle. Three patients showed a marked increase in mean PCW, whereas the remaining six patients showed only minor changes. The three patients who had a marked increment in mean PCW also worsened by one or two NYHA functional classes on clinical evaluation (table 1) (two patients from class II to class III and IV, respectively; one patient from class III to class IV). For all other patients who underwent sequential hemodynamic studies, functional class remained unchanged (table 1) (three patients in class I and three patients in class II).

Hemodynamic data: exercise. Exercise hemodynamic variables were recorded under control conditions (n = 9) and after 5 weeks of oral amiodarone treatment (n = 7) (see table 3). Two patients could no longer exercise during amiodarone treatment because of markedly increased PCW at rest, which caused orthopnea when the legs were raised to strap the feet to the bicycle. During amiodarone treatment, the remaining seven patients exercised at the same workloads as in the control run. For three of them, the duration of exercise was unaltered, whereas four of them stopped exercising earlier than in the control run. Because of the reduced exercise tolerance during amiodarone treatment in four patients, exercise data recorded before and during amiodarone treatment were compared in two ways. The hemodynamic data recorded at maximal exercise level during amiodarone treatment were compared with hemodynamic data recorded at the identical exercise level in the control run. Hemodynamic data recorded at the maximal exercise level during amiodarone treatment were also compared with hemodynamic data obtained at maximal exercise in the control run. At the maximal symptom-limited exercise level (EX II), mean PCW and mean PAP rose from 26 ± 10 to 37 ± 9 mm Hg (p < .005) and from 42 ± 19 to 51 ± 18 mm Hg (p < .01) during long-term amiodarone treatment. At the maximal symptom-limited exercise level, heart rate, mean systemic arterial pressure, and cardiac output were the same in the two exercise tests. There was a nonsignificant drop in exercise factor from 4.8 ± 2.0 to 3.5 ± 2.0 during amiodarone treatment.

The individual values of mean PCW at rest and maximal symptom-limited exercise are shown in figure 1 for the control exercise test and the exercise test.
TABLE 3

Hemodynamic data during exercise

<table>
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<tr>
<th>Patient</th>
<th>Heart rate (beats/min)</th>
<th>PAP (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>SAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EX I</td>
<td>EX II</td>
<td>EX I</td>
<td>EX II</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>C</td>
<td>Am</td>
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<tr>
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<td>117±17</td>
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<tr>
<td></td>
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<td>p&lt;.01</td>
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</table>

PAP = mean pulmonary artery pressure; PCW = mean pulmonary capillary wedge pressure; SAP = mean systemic arterial pressure; EX I = exercise comparison I, hemodynamic data at highest identical exercise level; EX II = exercise comparison II, hemodynamic data at symptom-limited maximal exercise level; C = control exercise test; Am = exercise test during amiodarone treatment.

recorded during amiodarone treatment. Two patients with the highest mean PCW at rest during amiodarone treatment could no longer exercise. Their individual values are presented by the two highest open points in the amiodarone rest columns (AM REST) in the middle and the right panels of figure 1. At the highest identical exercise level there was an even greater increase during amiodarone treatment in mean PCW and in mean PAP from 22 ± 8 to 37 ± 9 mm Hg (p < .001) and from 37 ± 15 to 51 ± 18 mm Hg (p < .01). At the highest identical exercise level, heart rate and systemic arterial pressure were comparable in the two exercise tests. The individual values of mean PCW at rest and at the highest identical exercise level are shown in figure 2, both for the control exercise test (left) and for the exercise test performed during amiodarone treatment (right).

Echocardiographic data. The noninvasive data obtained under control conditions and during long-term amiodarone treatment are summarized in table 4. Representative tracings from mitral valve echocardiograms and left ventricular cavity echocardiograms from which IVRT and dPW/dt were measured are shown in figure 3. The left panel shows diastolic portions of the mitral valve echocardiogram and the left ventricular cavity echocardiogram under control conditions, the right panel during long-term amiodarone treatment.

During long-term amiodarone treatment there is a significant prolongation of the RR interval from 805 ± 99 to 846 ± 166 msec (n = 11; p < .05). End-diastolic wall thickness, end-systolic wall thickness, and left ventricular relaxation indexes such as IVRT and dPW/dt remained unaltered during long-term amiodarone treatment. For patients with severe SAM, an index value of SAM was calculated before and during long-term amiodarone therapy (table 1). For two patients this index increased from 2.9 to 4.0 and from 1.0 to 1.5; for one patient this index decreased from 2.8 to 2.0.

Discussion

In recent years, amiodarone has received widespread attention as a valuable therapeutic adjunct to the medical management of patients with hypertrophic cardiomyopathy. The drug has been shown to be effective as an antiarrhythmic agent for the treatment of ventricular arrhythmias, and when compared with conventional class I antiarrhythmic agents it was shown to improve survival in patients with hypertrophic cardiomyopathy. Left ventricular function studies during long-term amiodarone treatment have been performed with serial radionuclide angiograms, which documented unaltered ejection fraction and left ventricular filling indexes in patients with hypertrophic cardiomyopathy and in patients with congestive car-
TABLE 3
(Continued)

<table>
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<tr>
<th>Cardiac output (l/min)</th>
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<td>9.5 ± 4.5</td>
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</table>

The present study on the influence of long-term amiodarone treatment in patients with hypertrophic cardiomyopathy, opposite results were obtained: amiodarone had a negative effect on rest and exercise hemodynamics, whereas echocardiographic relaxation indexes remained unaltered. The severity and nature of symptoms, the stress testing protocol, and the presence of arrhythmias could account for the observed discrepancies in amiodarone's effect on left ventricular function in patients with hypertrophic cardiomyopathy.

The cause of symptoms in hypertrophic cardiomyopathy is thought to be multifactorial: decreased diastolic distensibility with blunted rapid left ventricular filling, the occurrence and magnitude of an outflow tract gradient, and the presence of myocardial ischemia. Moreover, certain pathophysiologic mechanisms such as myocardial ischemia and decreased left ventricular distensibility interact.33, 37 Because of the multifactorial origin of symptoms, the benefit of a therapeutic intervention depends on the prevailing symptom and the severity of symptoms in the study group. When most patients in a study population stop exercising because of angina, an agent like amiodarone, which possesses mild anti-ischemic and β-blocking properties, might cause an overall symptomatic benefit. Such effect is unlikely to occur when dyspnea is the predominant limiting symptom during exercise. In such an instance a drug that fails to correct left ventricular diastolic properties is unlikely to be of symptomatic benefit. In our study, eight of nine patients had no or mild symptoms on clinical evaluation at the time of the control studies and most of them were

TABLE 4
Echocardiographic data

<table>
<thead>
<tr>
<th>RR interval (msec)</th>
<th>IVRT (msec)</th>
<th>PWTD (cm)</th>
<th>PWTs (cm)</th>
<th>dPW/dt (mm/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>C</td>
<td>Am</td>
<td>C</td>
<td>Am</td>
</tr>
<tr>
<td>1</td>
<td>680</td>
<td>877</td>
<td>67</td>
<td>111</td>
</tr>
<tr>
<td>2</td>
<td>873</td>
<td>1231</td>
<td>110</td>
<td>129</td>
</tr>
<tr>
<td>3</td>
<td>760</td>
<td>680</td>
<td>69</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>916</td>
<td>925</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>878</td>
<td>805</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>805</td>
<td>740</td>
<td>105</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>835</td>
<td>950</td>
<td>95</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>960</td>
<td>710</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>819</td>
<td>860</td>
<td>71</td>
<td>65</td>
</tr>
<tr>
<td>10</td>
<td>483</td>
<td>578</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>724</td>
<td>830</td>
<td>64</td>
<td>68</td>
</tr>
<tr>
<td>805</td>
<td>846</td>
<td>78</td>
<td>82</td>
<td>1.1</td>
</tr>
<tr>
<td>± 99 ± 166</td>
<td>± 23 ± 26</td>
<td>± 0.1 ± 0.1</td>
<td>± 0.2 ± 0.2</td>
<td>± 47 ± 51</td>
</tr>
<tr>
<td>p&lt;.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

PWTD = diastolic posterior wall thickness; PWTs = systolic posterior wall thickness.

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limited during exercise testing by dyspnea (table 1). A different therapeutic result could be obtained in a study population that is more severely symptomatic and whose predominant symptom is angina.

In the present study, all patients underwent supine bicycle exercise stress testing. In previous reports on exercise tolerance during long-term amiodarone treatment in patients with hypertrophic cardiomyopathy, a treadmill exercise test was used. During a supine bicycle exercise test there is a larger increase in venous return. Whenever there is a pathologic response to exercise, left ventricular filling pressures will therefore be augmented more rapidly during supine bicycle exercise stress testing, with the earlier occurrence of dyspnea and a concomitant reduction in exercise tolerance. This abnormal exercise physiology will be more evident when abnormal diastolic properties are prominent, as in hypertrophic cardiomyopathy. In fact, the present and similar studies showed increased PCW during supine bicycle exercise stress testing in patients with hypertrophic cardiomyopathy with normal exercise tolerance and minimal or no symptoms. In supine bicycle exercise stress testing, there is improved exercise tolerance during therapy with verapamil, probably because of improved diastolic properties, but not during therapy with propranolol.

**FIGURE 1.** Individual values of mean PCW at rest (REST) and at maximal symptom-limited exercise level (EX II) under control conditions before treatment (C) and during long-term amiodarone treatment (AM).

**FIGURE 2.** Individual values of mean PCW at rest (REST) and at the highest identical exercise level (EX I) under control conditions before treatment (C) and during long-term amiodarone treatment (AM).
THERAPY AND PREVENTION–HYPERTROPHIC CARDIOMYOPATHY

Under such exercising conditions, a beneficial anti-ischemic effect of a drug such as a β-blocking agent or amiodarone is probably offset by its negative inotropic effect. This negative inotropic effect causes a compensatory rise in left ventricular filling pressure to maintain cardiac output. When the left ventricle is hypertrophied and stiff and when it faces a larger volume load induced by bicycle stress testing in a supine position, the rise in left ventricular filling pressures will be larger, leading to earlier occurrence of symptoms and a concomitant reduction in exercise tolerance. The discrepancy between our results and those of other reports\textsuperscript{22, 23} on exercise tolerance in patients with hypertrophic cardiomyopathy during long-term amiodarone treatment could be similar to the discrepancy between reports on exercise tolerance in patients with hypertrophic cardiomyopathy during β-blockade, in that a supine bicycle stress test failed to document the improved exercise tolerance\textsuperscript{3} that was observed with an upright stress test.\textsuperscript{2}

In the present study, all patients were in sinus rhythm with no or low-grade ventricular arrhythmias. This excludes the confounding influence of improved arrhythmia control on hemodynamic measurements during long-term amiodarone treatment. Both the decrease in resting heart rate and the elevated filling pressures during amiodarone treatment could influence echocardiographic indexes of left ventricular relaxation such as IVRT and left ventricular filling or wall thinning rates. IVRT was previously found to be independent of heart rate in a study on the influence of β-blocking drugs on left ventricular diastolic properties in patients with hypertrophic cardiomyopathy.\textsuperscript{5} An elevation of left ventricular filling pressures causes premature opening of the mitral valve and shortens IVRT. During long-term amiodarone treatment IVRT remained unaltered despite elevated PCW. This finding suggests a slower decay of isovolumic pressure as a result of long-term amiodarone treatment. In previous studies in normal subjects there was no correlation between heart rate at rest over a range varying from 44 to 99 beats/min and peak left ventricular filling rate.\textsuperscript{38} The decrease in heart rate (from 80 to 75 beats/min; p < .05) observed in our study during long-term amiodarone treatment falls within this range.

Echocardiographic indexes of left ventricular filling such as peak filling rate or dPW/dt were shown to be dependent on shortening fraction\textsuperscript{38} or on extent of wall thickening.\textsuperscript{39} Other investigators using radionuclide left ventricular angiograms normalized left ventricular volumes by end-diastolic volume.\textsuperscript{12, 37} In the present study there was no significant change during long-term amiodarone treatment in the extent of wall thickening or end-diastolic wall thickness. On the other hand, left ventricular filling pressure (measured as mean PCW) was significantly elevated during long-term amiodarone treatment. This elevation of diastolic pressure did not cause an appreciable change in echocardiographic end-diastolic wall thickness, probably because of the steep compliance curve of the hypertrophied left ventricle,\textsuperscript{40} but could have influenced posterior wall thinning rates.

FIGURE 3. Echocardiograms at the level of the mitral valve and at the level of the left ventricular cavity obtained before (left) and during long-term amiodarone therapy (right). IVRT was calculated as the interval between the first high-frequency components of the aortic valve closure sound (A2) (vertical line) and mitral valve opening on the mitral valve echocardiogram. dPW/dt was derived from the diastolic motion of the posterior wall in the left ventricular cavity echocardiogram. IVS = interventricular septum; MV = mitral valve; PW = posterior wall.
In experiments with isolated cardiac muscle, lengthening velocity was a function of end-systolic length and lengthening load. Under controlled loading conditions such as those that occur in isolated muscle experiments, lengthening load equals diastolic load and determines end-diastolic dimension in accordance with the passive length-tension characteristics of the muscle preparation. Therefore lengthening load and end-diastolic dimension are considered to be interchangeable as determinants of muscle lengthening. However, when diastolic load varies, as always occurs during filling of the intact heart, the same relationship no longer holds. In such instances wall stress at peak filling rate is the determinant of myocardial lengthening and not end-diastolic dimension. Wall stress itself is determined both by filling pressure and by instantaneous left ventricular dimensions. In the present study, during long-term amiodarone treatment left ventricular dimensions were comparable to control data but filling pressures were significantly elevated. Therefore wall stress during filling was probably elevated. Under conditions of elevated diastolic wall stress during long-term amiodarone treatment, peak posterior wall thinning rate should increase if myocardial inactivation and end-systolic dimensions remain unaltered. In the present study, however, we observed no change in peak posterior wall thinning rate despite elevated diastolic left ventricular filling pressures and unaltered end-systolic wall thickness during long-term amiodarone therapy. This result could imply a worsening of myocardial inactivation by amiodarone, whose effect on left ventricular filling is partially corrected by the elevated left ventricular filling pressures and therefore results in unaltered echocardiographic left ventricular filling indexes.

There are no experimental data concerning the influence of long-term amiodarone on isolated cardiac muscle relaxation. The drug’s intrinsic properties are suggestive of a hypothyroid state of the heart, e.g., sinus bradycardia through sinus node depression, reduced myocardial oxygen demand independent of sinus bradycardia, and prolongation of the corrected QT interval. In hypothyroid heart disease, an impairment of left ventricular relaxation has previously been demonstrated and explained by deficient calcium reuptake of the sarcoplasmic reticulum. This mechanism also accounts for slow striated muscle relaxation, which causes the characteristic slow tendon reflexes of hypothyroidism. A hypothyroid state of the heart induced by long-term amiodarone treatment could explain a depressant effect of amiodarone on myocardial inactivation.

Amiodarone exhibits a noncompetitive blockade of both α- and β-adrenergic receptors. Its alphalytic action could lead to peripheral vasodilatation, which was observed after short-term intravenous administration in some studies but not confirmed by others. During long-term administration no significant change in systemic vascular resistance was demonstrated in patients with coronary disease or in the present study in patients with hypertrophic cardiomyopathy. However, a progressive drop in systemic vascular resistance was observed in patients with congestive failure from chronic Chagas disease. Such a vasodilatory effect warrants caution, especially in patients with an obstructive form of hypertrophic cardiomyopathy. In the present study, two patients with severe SAM had evidence of an earlier onset of mitral leaflet–septal contact on the mitral valve echocardiogram during long-term amiodarone treatment (table 1, patients 6 and 11). An earlier onset of mitral leaflet–septal contact argues in favor of an increment in outflow tract gradient, which could also affect left ventricular isovolumic relaxation by altering end-systolic loading conditions. Definitive evidence for a change in magnitude of the outflow tract gradient during long-term amiodarone treatment requires repeat left-heart catheterization, which was not performed in this study. Apart from its alphalytic properties, amiodarone also blocks β-adrenergic receptors. The effects of β-blockade on exercise tolerance and diastolic properties in patients with hypertrophic cardiomyopathy remain controversial.

In summary, long-term treatment with amiodarone in patients with hypertrophic cardiomyopathy caused a small but significant increase in left ventricular filling pressures at rest. Exercise tolerance assessed by repeat supine bicycle stress testing was reduced in most patients because of higher PCW pressures at identical workloads. The worsened rest and exercise hemodynamics are consistent with a negative inotropic action of amiodarone. Echocardiographic relaxation indexes such as IVRT and dP/dt remained unaltered during long-term amiodarone treatment despite an elevation of left ventricular filling pressures. This finding suggests an impairment of myocardial inactivation induced by long-term amiodarone treatment. Such impairment is possibly similar in mechanism to the depressed myocardial inactivation observed in hypothyroidism.

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