Amiodarone Improves Cardiac Sympathetic Nerve Function to Hold Norepinephrine in the Heart, Prevents Left Ventricular Remodeling, and Improves Cardiac Function in Rat Dilated Cardiomyopathy

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Background—It is unclear how amiodarone therapy exerts its effects on left ventricular remodeling and cardiac sympathetic nerve function in chronic heart failure. We investigated long-term effects of amiodarone on rat dilated cardiomyopathy after healing of cardiac myosin–induced autoimmune myocarditis.

Methods and Results—Rats were treated with oral amiodarone or vehicle for 6 weeks. We determined cardiac function, left ventricular remodeling, and cardiac sympathetic nerve function with iodine-125–labeled metaiodobenzylguanidine ([I\(^{125}\)]MIBG). Amiodarone treatment improved left ventricular pressure, central venous pressure, and rate of isovolumetric contraction and decreased ventricular weight (\(P<0.005\)). Expression of cytokine mRNA was unchanged; expression of atrial natriuretic peptide, collagen III, and transforming growth factor-\(\beta_1\) mRNA was decreased in amiodarone-treated rats (\(P<0.05\)). Phenotype of myosin heavy chain was moved toward that of normal rats by amiodarone. Initial myocardial uptake of MIBG decreased by 67% (\(P<0.001\)) and washout rate accelerated by 221% in rats with chronic heart failure compared with normal rats. Whereas amiodarone decreased the initial uptake by 71% in normal rats, amiodarone decelerated the early washout and the late washout and improved the late myocardial distribution of MIBG in rats with chronic heart failure (257% compared with vehicle-treated rats with chronic heart failure; \(P<0.01\)). In proportion to MIBG distributions, cardiac tissue catecholamines were increased by amiodarone treatment.

Conclusions—Long-term amiodarone treatment prevented left ventricular remodeling and improved cardiac function in rat dilated cardiomyopathy. Long-term amiodarone treatment also restored cardiac sympathetic tone to hold norepinephrine in the heart. (Circulation. 2005;111:894-899.)

Key Words: cardiomyopathy | antiarrhythmia agents | remodeling | nervous system, sympathetic

Sudden cardiac death and progressive deterioration of left ventricular function remain major clinical problems in the management of heart failure. \(\beta\)-Blockers and angiotensin-converting enzyme inhibitors improve functional status and reduce mortality in patients with heart failure. Amiodarone has already been shown to be efficacious for ventricular arrhythmia in patients with left ventricular dysfunction. The results obtained from clinical trials are controversial with regard to the efficacy of amiodarone in heart failure.\(^{1-6}\) Favorable outcomes of amiodarone treatment on mortality and on left ventricular function were shown in some selected patients,\(^{2,3}\) although the amount of benefit remains imprecise. Recent trials could not show additional efficacy except for decrease of heart rate, prevention of lethal arrhythmias, and improvement of cost-effectiveness.\(^{4-6}\) Discordances among those results may depend on the pleiotropic actions of amiodarone. The precise mechanisms of the beneficial actions of amiodarone on chronic heart failure are still uncertain.

The specific causes of heart failure may characterize the nature of left ventricular remodeling, clinical course, and response to therapy. Rat experimental autoimmune myocarditis leads to chronic heart failure such as dilated cardiomyopathy after healing of the inflammation.\(^7\) Amiodarone has been studied in several animal models, showing some beneficial effects,\(^{5-10}\) but the manner in which amiodarone improves cardiac function or heart failure remains to be clarified. In the present study we assessed the effects of

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amiodarone on left ventricular remodeling and cardiac function in inflammatory cardiomyopathy.

Single-photon emission CT imaging with the use of radioiodinated metaiodobenzylguanidine (MIBG), an analogue of norepinephrine with the same affinity for the sympathetic nervous system, enables quantitative assessment of norepinephrine behavior as a result of release and reuptake at the adrenergic presynaptic site. The myocardial accumulation of MIBG and its washout rate from the heart are useful indicators to evaluate the severity of dilated cardiomyopathy and the response to therapy with β-blockers.11–13

The purpose of the present study is to examine in vivo effects of amiodarone on left ventricular remodeling, cardiac hemodynamics, and cardiac sympathetic function in an animal model of inflammatory cardiomyopathy.

Methods

Experimental Animals

Male Lewis rats (aged 8 weeks) were purchased from Charles River, Japan (Yokohama, Japan) and maintained in our facilities. Experimental autoimmune myocarditis was induced by immunization with purified pig cardiac myosin as previously described.14 Rats surviving 28 days after immunization were allocated to the study groups. We treated rats for 6 weeks until day 70 and evaluated them at day 73. The study protocol was conducted according to the guidelines on animal experimentation of our institute.

Experiment 1

First, we examined the effects of amiodarone on left ventricular remodeling and cardiac function. We designed the following groups: rats with chronic heart failure treated with very-low-dose amiodarone (5 mg/kg daily; amiodarone 5 mg group; n = 8); rats with chronic heart failure treated with regular-dose amiodarone (50 mg/kg daily; amiodarone 50 mg group; n = 8); rats with chronic heart failure treated with vehicle alone (methylcellulose 0.5 mL daily; vehicle group; n = 8); and age-matched normal control rats (NC group; n = 4).

Cardiac Function Assessment

ECG (SP-98, Softron) was recorded before (at day 28) and during treatment (at day 50, 3 weeks after the start of treatment). Rats were anesthetized with ether. At day 73, rats were anesthetized with 0.5% halothane mixed with 100% oxygen, and systemic and left ventricular hemodynamic parameters were recorded as described previously.15,16 Blood samples were obtained from the inferior vena cava to measure serum concentration of amiodarone and thyroid hormone. The ventricle was excised and weighed. The mid-ventricle was quickly excised and stored in a gamma counter tube, and MIBG and its washout rate from the heart are useful indicators to evaluate the severity of dilated cardiomyopathy and the response to therapy with β-blockers.11–13

The purpose of the present study is to examine in vivo effects of amiodarone on left ventricular remodeling, cardiac hemodynamics, and cardiac sympathetic function in an animal model of inflammatory cardiomyopathy.

**TABLE 1. Ventricular Weight, Cardiomyocyte Width, and Myocardial Fibrosis**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Plasma Amiodarone, µmol/L</th>
<th>Serum-Free Triiodothyronine, pmol/L</th>
<th>Body Weight, g</th>
<th>Ventricle Weight, g</th>
<th>Ventricle Weight/Body Weight, g/kg</th>
<th>Cardiomyocyte Width, µm</th>
<th>Endocardium</th>
<th>Epicardium</th>
<th>Fibrosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>4</td>
<td>...</td>
<td>...</td>
<td>441.2 ± 17.1†</td>
<td>1.22 ± 0.05†</td>
<td>2.27 ± 0.09†</td>
<td>13.4 ± 0.2†</td>
<td>13.8 ± 0.2†</td>
<td>3.3 ± 0.3†</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>8</td>
<td>ND</td>
<td>4.03 ± 0.34</td>
<td>347.3 ± 14.4</td>
<td>1.42 ± 0.04</td>
<td>4.13 ± 0.16</td>
<td>22.9 ± 0.6</td>
<td>23.9 ± 0.7</td>
<td>24.6 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>Amiodarone 5 mg</td>
<td>8</td>
<td>ND</td>
<td>4.42 ± 0.49</td>
<td>349.6 ± 13.4</td>
<td>1.43 ± 0.05</td>
<td>4.11 ± 0.16</td>
<td>22.3 ± 1.7</td>
<td>23.8 ± 2.0</td>
<td>27.1 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>Amiodarone 50 mg</td>
<td>8</td>
<td>0.938 ± 0.015</td>
<td>3.51 ± 0.15</td>
<td>353.7 ± 8.5</td>
<td>1.16 ± 0.06*</td>
<td>3.26 ± 0.11†</td>
<td>18.1 ± 1.2†</td>
<td>20.1 ± 1.6</td>
<td>20.2 ± 3.1</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± SE. ND indicates not detectable.

*P<0.005, †P<0.001, ‡P<0.05 vs CHF group.
Nichion Chemical) and centrifuged at 14 000 rpm for 10 minutes at 4°C. The supernatant was used for the assay. Concentrations of epinephrine and norepinephrine in myocardial tissue were measured by high-performance liquid chromatography (PLC-725CAH, Tosco Co). Concentrations of IL-6 and TNF-α in myocardial tissue were also measured by enzyme-linked immunosorbent assay with commercially available kits (Genzyme Corporation). The procedures were performed according to the manufacturer’s recommendations. The total protein concentration in supernatant was measured by the Pierce bicinchoninic acid protein quantification assay (Pierce Chemical Co).

Statistical Analysis

Results are presented as mean±SEM. Statistical significance was determined by 1-way ANOVA followed by the Fisher protected least significant difference method. In all tests, statistical significance was assumed at an α value of 0.05.

Results

No rats died during the chronic phase after day 28. The RR, PR, and QRS intervals were not different among the 3 groups. The QT interval was prolonged in the amiodarone 50 mg group compared with the CHF group (100.2±2.1 versus 85.4±4.0 ms; P<0.01). RR interval was also prolonged in the amiodarone 50 mg group, but the difference was not significant (206.4±8.6 versus 173.0±9.1 ms). Serum concentration of amiodarone was high in the amiodarone 50 mg group but was not detectable in the amiodarone 5 mg and CHF groups. Serum concentration of free triiodothyronine was not different among the 3 groups (Table 1).

Cardiac Function and Neurohumoral Parameters

Hemodynamic parameters are shown in Table 2. In the amiodarone 50 mg group, systemic arterial pressure increased and central venous pressure was decreased compared with the CHF group. The absolute value of the rate of isovolumetric contraction was also higher in the amiodarone 50 mg group than in the CHF group.

Myocardial expression of r-ANP mRNA was lower in the amiodarone 50 mg group than in the CHF group (Table 3). Myocardial MHC phenotype changed according to deterioration of left ventricular function and improvement by therapy (Figure 1 and Table 3). In the amiodarone 50 mg group, α-MHC mRNA expression increased, β-MHC mRNA expression decreased, and the ratio of α-MHC to β-MHC increased. The amiodarone 5 mg group showed no significant changes compared with the CHF group in hemodynamic parameters except for systolic and mean arterial pressure, but the ratio of α-MHC to β-MHC increased.

### Table 2. Hemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>NC (n=4)</th>
<th>CHF (n=8)</th>
<th>Amiodarone 5 mg (n=8)</th>
<th>Amiodarone 50 mg (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>314.4±22.6</td>
<td>307.2±23.2</td>
<td>315.7±28.0</td>
<td>319.9±16.6</td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>109.5±7.0</td>
<td>64.6±4.9*</td>
<td>89.1±8.3†</td>
<td>91.6±6.3‡</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98.3±6.5</td>
<td>57.4±4.8*</td>
<td>83.0±7.9†</td>
<td>84.2±6.1‡</td>
</tr>
<tr>
<td>Left ventricular pressure, mm Hg</td>
<td>90.4±5.5</td>
<td>68.7±2.5†</td>
<td>79.6±8.1</td>
<td>85.9±5.3‡</td>
</tr>
<tr>
<td>Central venous pressure, mm Hg</td>
<td>1.2±0.2</td>
<td>5.6±1.1†</td>
<td>5.6±1.6</td>
<td>1.7±0.6§</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure, mm Hg</td>
<td>7.6±1.6</td>
<td>18.9±3.5†</td>
<td>19.9±6.3</td>
<td>13±2.4</td>
</tr>
<tr>
<td>+dP/dt, mm Hg/s</td>
<td>3923±575.0</td>
<td>2409±252.5</td>
<td>2486±371.5</td>
<td>3520±205.7‡</td>
</tr>
<tr>
<td>−dP/dt, mm Hg/s</td>
<td>−4741±701.1</td>
<td>−2488±445.1†</td>
<td>−2192±239.6</td>
<td>−3169±214.0</td>
</tr>
</tbody>
</table>

Values are mean±SE. +dP/dt indicates rate of isovolumetric contraction; −dP/dt, rate of isovolumetric relaxation.

*P<0.001, †P<0.05 vs NC group; ‡P<0.05 vs CHF group; §P<0.05 vs amiodarone 5 mg group.

### Table 3. Myocardial Tissue mRNA Expression

<table>
<thead>
<tr>
<th></th>
<th>NC (n=4)</th>
<th>CHF (n=8)</th>
<th>Amiodarone 5 mg (n=8)</th>
<th>Amiodarone 50 mg (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial natriuretic peptide, 10⁶ molecules mRNA/μg of total RNA</td>
<td>4.1±1.4</td>
<td>83.8±15.1*</td>
<td>82.4±11.7</td>
<td>43.9±9.7†</td>
</tr>
<tr>
<td>Sarcoplasmic reticulum calcium ATPase, 10⁶ molecules mRNA/μg of total RNA</td>
<td>454±126</td>
<td>418±161</td>
<td>212±40</td>
<td>306±62</td>
</tr>
<tr>
<td>Collagen III, 10⁶ molecules mRNA/μg of total RNA</td>
<td>39±12</td>
<td>494±157*</td>
<td>474±72</td>
<td>174±33</td>
</tr>
<tr>
<td>TNF-α, 10⁶ molecules mRNA/μg of total RNA</td>
<td>0.08±0.02</td>
<td>0.22±0.05†</td>
<td>0.25±0.03</td>
<td>0.20±0.02</td>
</tr>
<tr>
<td>TGF-β, 10⁶ molecules mRNA/μg of total RNA</td>
<td>3.4±1.0</td>
<td>5.2±0.7</td>
<td>4.1±0.2</td>
<td>3.0±0.3§</td>
</tr>
<tr>
<td>MHC α-Myosin, 10⁶ molecules mRNA/μg of total RNA</td>
<td>439±143</td>
<td>85±37*</td>
<td>79±7</td>
<td>115±21</td>
</tr>
<tr>
<td>β-Myosin, 10⁶ molecules mRNA/μg of total RNA</td>
<td>227±54</td>
<td>116±56</td>
<td>85±13</td>
<td>109±30</td>
</tr>
<tr>
<td>Total, 10⁶ molecules mRNA/μg of total RNA</td>
<td>666±195</td>
<td>251±87†</td>
<td>164±19</td>
<td>224±50</td>
</tr>
<tr>
<td>Proportion α-myosin, %</td>
<td>63.5±3.5</td>
<td>31.4±4.8*</td>
<td>48.9±1.6§</td>
<td>52.5±3.0§</td>
</tr>
<tr>
<td>Proportion β-myosin, %</td>
<td>36.4±3.5</td>
<td>68.6±4.8*</td>
<td>51.0±1.6§</td>
<td>47.4±3.0§</td>
</tr>
<tr>
<td>α-Myosin/β-myosin</td>
<td>1.81±0.27</td>
<td>0.48±0.11*</td>
<td>0.96±0.06‡</td>
<td>1.16±0.14§</td>
</tr>
</tbody>
</table>

Values are mean±SE.

*P<0.001, †P<0.05 vs NC group; ‡P<0.05, §P<0.005 vs CHF group; ||P<0.05 vs amiodarone 5 mg group.
In the present study amiodarone prevented left ventricular remodeling and improved cardiac function in rat dilated 

**Figure 2.** Myocardial histopathological changes in rats with chronic heart failure. Widespread fibrosis and various sizes of cardiomyocytes were observed in rats with chronic heart failure. Cardiomyocytes were smaller and more homogeneous in rats with heart failure treated with regular dose of amiodarone (Amio50) (hematoxylin-eosin stain; magnification ×400.) Amio5 indicates chronic heart failure rat treated with amiodarone 5 mg/kg daily; Amio50, chronic heart failure rat treated with amiodarone 50 mg/kg daily.

**Figure 3.** Autoradiographic images of ventricular MIBG distribution.

The myocardial uptake of MIBG was lower in the CHF group (Figure 4 and Table 4). The early WR (WR1) was similar between the CHF and the NC groups, whereas the late WR (WR2) and total WR were markedly accelerated and the late accumulation at 240 minutes was significantly less in the CHF group compared with the NC group.

Long-term amiodarone treatment decreased the initial uptake at 10 minutes in normal rats. The early WR (WR1) was markedly decreased by amiodarone treatment in both normal rats and rats with chronic heart failure, and the accumulation at 30 minutes increased relative to the baseline at 10 minutes. The late WR (WR2) was also decreased in the CHF+A group, and the late accumulation (240 minutes) was higher than that seen in the CHF group.

Cardiac tissue catecholamines, initially at low levels in rats with chronic heart failure, increased after amiodarone treatment (Figure 4 and Table 4). Long-term amiodarone treatment increased cardiac tissue norepinephrine and epinephrine levels in normal rats and rats with chronic heart failure.

**Discussion**

In the present study amiodarone prevented left ventricular remodeling and improved cardiac function in rat dilated
cardiomyopathy after autoimmune myocarditis. Restoring the ratio of α-MHC to β-MHC (α/β) by increasing the expression level of α-MHC mRNA and decreasing that of β-MHC may contribute to improved cardiac function. A recent report showed that β-MHC mRNA decreased independent of the improvement of cardiac function in patients with dilated cardiomyopathy who were treated with a β-blocker.19 We cannot answer whether the modulation of gene expression profiles observed in this study is caused by the direct action of amiodarone or the improvement of heart failure. Our study also showed a significant decrease of TGF-β1 expression by amiodarone treatment, which might partially contribute to the phenotypic change of MHC. In contrast, there were no differences in the myocardial TNF-α and IL-6 levels with or without amiodarone despite persistent expression of some inflammatory cytokines. TNF-α may directly contribute to the deterioration of heart function. A clinical trial subanalysis indicated that the efficacy of amiodarone in heart failure may be partly related to inhibiting production of TNF-α.20 Recent studies showed that amiodarone modulates the production of TNF-α and IL-6, which may attenuate myocardial injury and prevent left ventricular remodeling in human and mouse myocarditis.10,21 Even though the drug exerted its expected biological effects, TNF-α antagonism failed to produce clinical benefits in patients with heart failure.22 We believe that the pathogenesis of the chronic phase of this rat model is ventricular remodeling in response to diffusely scattered myocardial fibrosis.7 Suppression of TGF-β1 seemed to be important in preventing left ventricular remodeling by long-term amiodarone treatment.

Our present study found a low initial uptake and a lower late accumulation of norepinephrine in rats with chronic heart failure. This faster washout may be attributed to increased norepinephrine spillover and clearance in chronic heart failure. The consequent cardiac catecholamine depletion may explain the low cardiac catecholamine levels shown in our present study. Amiodarone increased cardiac catecholamine levels to restore adrenergic order in both normal and CHF rats. MIBG WR was also decreased; these results were similar to the findings demonstrated by Kaye et al23 that amiodarone improved cardiac sympathetic nerve function with a low cardiac norepinephrine spillover rate in patients with heart failure.

It is interesting that amiodarone shifts the peak accumulation from 10 to 30 minutes. This effect on MIBG kinetics was observed in both normal rats and CHF rats, and it is an identical effect of amiodarone. There are 2 mechanisms for the shift of the peak. One is that the initial uptake of MIBG is delayed by amiodarone. The uptake-2 system must be delayed mainly because the uptake-2 system is passive diffusion with rapid turnover, whereas the uptake-1 system is long-lasting filling into the storage vesicle.24,25 Another mechanism is that amiodarone enhances the uptake-1 system. The uptake-1 system has a dual mechanism of reuptake and release, and the vesicular storage is mediated by a reversed neuronal reuptake mechanism that is enhanced by inhibition of the sodium-potassium adenosine triphosphatase "pump" in myocardial ischemia.26,27 Amiodarone accelerated WR2 in the normal rats; however, the uptake may prevail and total WR may be decreased, resulting in holding norepinephrine in the heart.

Central and peripheral actions of amiodarone on cardiovascular autonomic nervous system have been reported.28–33 The antiadrenergic effect of amiodarone is, however, different from that of β-blockers because amiodarone is noncompetitive and additive to the effects of β-blockers.29,30 Amiodarone has various effects on sympathetic and vagal activity, such as direct Na+ and Ca2+ channel-blocking properties,31 inhibition of the muscarinic acetylcholine receptor–operated K+ current,32 and reserpine-like sympatholytic action.33 These effects may depress the automaticity of sinus node and sympathetic tone. Du et al33 observed hypotension, decreased heart rate, and depressed inotropic response of the ventricle to sympathetic activation after intravenous amiodarone admin-

TABLE 4. Cardiac Tissue Catecholamine Concentration, MIBG Accumulation, and WR

<table>
<thead>
<tr>
<th>Group</th>
<th>Epinephrine, pg/g protein</th>
<th>Norepinephrine, pg/g protein</th>
<th>10 Minutes (a)</th>
<th>30 Minutes (b)</th>
<th>240 Minutes (c)</th>
<th>WR1 (a−b)/a, %</th>
<th>WR2 (b−c)/a, %</th>
<th>Total WR (a−c)/a, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC</td>
<td>39.7±14.3 (n=5)</td>
<td>3107.8±946.2 (n=5)</td>
<td>11.55±0.86 (n=7)</td>
<td>9.50±0.66 (n=4)</td>
<td>7.70±0.54 (n=8)</td>
<td>17.7</td>
<td>18.9</td>
<td>33.3</td>
</tr>
<tr>
<td>N+A</td>
<td>156.0±24.9* (n=5)</td>
<td>5878.4±522.9† (n=5)</td>
<td>8.30±1.06† (n=4)</td>
<td>9.41±0.46 (n=4)</td>
<td>6.04±0.94 (n=4)</td>
<td>−13.3</td>
<td>35.8</td>
<td>22.8</td>
</tr>
<tr>
<td>CHF</td>
<td>4.2±2.2† (n=5)</td>
<td>64.5±67.8† (n=5)</td>
<td>7.84±1.04* (n=7)</td>
<td>6.37±0.73 (n=4)</td>
<td>2.05±0.35§ (n=7)</td>
<td>18.7</td>
<td>67.8</td>
<td>73.8</td>
</tr>
<tr>
<td>CHF+A</td>
<td>29.8±7.4§ (n=5)</td>
<td>1080.9±208.2† (n=5)</td>
<td>7.52±0.89 (n=7)</td>
<td>7.91±0.43 (n=4)</td>
<td>5.27±1.29§ (n=5)</td>
<td>−5.1</td>
<td>33.4</td>
<td>29.9</td>
</tr>
</tbody>
</table>

Values are mean±SE.
*P<0.001, †P<0.005, §P<0.05 vs normal control group; ¶P<0.01, ‡P<0.005 vs CHF group.
stration. In our present study long-term amiodarone treatment improved the left ventricular systolic function, as shown by the increase of positive dP/dt. It is possible that holding norepinephrine in the heart and a change of cardiac myosin phenotype may contribute to enforcing cardiac contractility to improve hemodynamic parameters. However, caution is necessary when the findings of this study obtained from rats are extrapolated into clinical practice because we have not examined this aspect in humans.

In conclusion, long-term amiodarone treatment suppressed left ventricular remodeling and improved cardiac function in rat dilated cardiomyopathy after autoimmune myocarditis. In vivo assessment of cardiac sympathetic nerve function with the use of MIBG showed a lower WR and an increased late accumulation of MIBG, which would hold norepinephrine in the heart. Thus, amiodarone treatment may be beneficial in chronic heart failure.

Acknowledgments
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References
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