Short-Term Amiodarone Treatment Attenuates the Production of Monocyte Cytokines and Chemokines by C-Reactive Protein and Improves Cardiac Function in Patients With Idiopathic Dilated Cardiomyopathy and Ventricular Tachycardia

Yasuhiro Hirasawa, MD; Akihiro Nakagomi, MD; Yoshinori Kobayashi, MD; Takao Katoh, MD; Kyoichi Mizuno, MD

Background: Increased expression of cytokines and chemokines has been observed in chronic heart failure (CHF). Amiodarone reduces circulating cytokine levels, so it may attenuate the production of monocyte cytokines and chemokines by C-reactive protein (CRP) and thus improve the left ventricular ejection fraction (LVEF) in dilated cardiomyopathy (DCM) patients with ventricular tachycardia (VT).

Methods and Results: Peripheral blood mononuclear cells (PBMCs) were stimulated by 25 μg/ml CRP in 23 patients with DCM, who were divided into 2 groups based on whether or not amiodarone was included in their treatment (Amiodarone group n=8; No amiodarone group n=15). Tumor necrosis factor (TNF)-α and monocyte chemoattractant protein (MCP)-1 on monocytes at baseline and after 4 weeks of treatment was measured by ELISA and expressed as mean±SD (pg·ml⁻¹·10⁻⁶ PBMCs). The LVEF and the CRP-induced monocyte cytokine and chemokine production were unchanged in the No amiodarone group after 4 weeks; however, LVEF in the Amiodarone group was increased (32.7±6.9 to 39.2±6.9%; P=0.005), and TNF-α and MCP-1 production in the Amiodarone group were decreased (P=0.012, respectively).

Conclusions: Amiodarone attenuates the production of monocyte cytokines and chemokines by CRP, and improves LVEF in CHF patients with VT. (Circ J 2009; 73: 639–646)

Key Words: Antiarrhythmia agents; Cardiomyopathy; Heart failure; Tachyarrhythmias

Ventricular tachyarrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF), in patients with chronic heart failure (CHF) are associated with an increased risk of mortality and sudden death. The GESICA trial demonstrated that amiodarone significantly reduces mortality and readmission because of worsening of heart failure in patients with CHF, although it does not reduce the incidence of sudden death. Moreover, in the CHF-STAT trial non-ischemic CHF patients in the amiodarone group showed a tendency for better prognosis than those in the placebo group, although as observed in the GESICA trial amiodarone did not reduce sudden death. These data suggest that amiodarone may improve the prognosis in CHF patients, independent of its antiarrhythmic activity.

It is now well accepted that CHF is associated with systemic inflammation, characterized by increased activation of proinflammatory cytokines and chemokines. Elevated levels of proinflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, and chemokines including MCP-1 and IL-8 are observed and associated with increased New York Heart Association (NYHA) functional class in CHF patients. The levels of these cytokines and chemokines are negatively correlated with the left ventricular ejection fraction (LVEF), which suggests that proinflammatory cytokines and chemokines may play significant roles in the pathogenesis and development of CHF.

Elevated plasma levels of C-reactive protein (CRP) have been observed and are predictive of poor outcomes in patients with cardiovascular diseases, including CHF; however, CRP has other specific functions, such as amplifying the production of monocyte proinflammatory cytokines such as TNF-α and IL-6 thus suggesting that CRP may not be simply a biomarker, but may play a significant role in the pathogenesis and development of CHF.

Matsumori et al showed that amiodarone decreases monocyte proinflammatory cytokine production in a dose-dependent manner in vitro; however, no previous studies have determined the in vivo effect of short-term amiodarone treatment on monocyte cytokine and chemokine production in CHF patients.

Therefore, the purpose of our study was to determine whether short-term amiodarone treatment attenuates the production of monocyte cytokines and chemokines by
CRP, while also improving LVEF in CHF patients with non-sustained ventricular tachycardia (NSVT).

**Methods**

**Study Subjects**

We studied 20 normal subjects (15 men, 5 women; mean age, 58.1±11.5 years), and 23 patients with idiopathic dilated cardiomyopathy (DCM: 18 men, 5 women; mean age, 63.9±5.9 years) who were admitted to hospital for heart failure management. DCM was defined as a normal coronary arteriogram together with severe hypokinesis of the left ventricular (LV) wall on left ventriculography and from typical pathological findings of an endomyocardial biopsy from the left ventricle. At baseline, the mean LVEF by echocardiography was 32.1±9.1%.

All patients were treated with standard medications, including optimal doses of β-blocking agents, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB) and diuretics, or a combination of these medications, for at least 4 weeks before enrollment, and all patients were stabilized on medications, so no medications had been changed prior to entry into the study. Anyone with clinical signs of acute infection, autoimmune disorders, acute myocardial infarction or unstable angina within the previous 12 months, severe renal (serum creatinine >5 mg/dl) or hepatic disease or with a suspected malignancy was excluded. In addition, any patient in the acute decompensated stage of CHF was excluded.

NSVT was defined as more than 6 ventricular premature contractions on Holter monitoring during the follow-up period, and amiodarone was administered to affected patients (Amiodarone group: n=8; No amiodarone group: n=15).

Patients in the Amiodarone group were given an oral loading dose of 200–400 mg daily for 2 weeks, then a maintenance dose of 100–200 mg/day for 4 weeks and in all patients the serum level of amiodarone reached 300–700 ng/ml.

The study protocol was consistent with the guidelines of the Institutional Ethics Committee of Nippon Medical School. All participants gave written informed consent.

**Reagents**

Human CRP (>95% pure) and Hanks’ balanced salt solution were obtained from Sigma (St Louis, MO, USA); RPMI 1640 was obtained from Gibco, and endotoxin-tested Lymphoprep was acquired from Nycomed Pharma AS. Human CRP (>95% pure) and Hanks’ balanced salt solution were obtained from Sigma (St Louis, MO, USA); RPMI 1640 was obtained from Gibco, and endotoxin-tested Lymphoprep was acquired from Nycomed Pharma AS. Human CRP (>95% pure) and Hanks’ balanced salt solution were obtained from Sigma (St Louis, MO, USA); RPMI 1640 was obtained from Gibco, and endotoxin-tested Lymphoprep was acquired from Nycomed Pharma AS. Human CRP (>95% pure) and Hanks’ balanced salt solution were obtained from Sigma (St Louis, MO, USA); RPMI 1640 was obtained from Gibco, and endotoxin-tested Lymphoprep was acquired from Nyomedis Pharma AS. Reagents

Venous peripheral blood was collected from all subjects and peripheral blood mononuclear cells (PBMCs) were isolated as described previously.14 In brief, PBMCs were obtained by gradient centrifugation on Lymphoprep and then incubated in serum-free RPMI at 37°C (in air containing 5% CO2).

**Laboratory Measurements**

Venous peripheral blood was collected from all subjects and peripheral blood mononuclear cells (PBMCs) were isolated as described previously.14 In brief, PBMCs were obtained by gradient centrifugation on Lymphoprep and then incubated in serum-free RPMI at 37°C (in air containing 5% CO2).

**Table 1. Clinical Characteristics of Normal Subjects and Patients With CHF**

<table>
<thead>
<tr>
<th></th>
<th>Normal (n=20)</th>
<th>CHF (n=23)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.1±11.5</td>
<td>63.9±9.9</td>
<td>0.087</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>15/5</td>
<td>18/5</td>
<td>0.801</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>119±8</td>
<td>116±8</td>
<td>0.318</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76±5</td>
<td>69±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70±6</td>
<td>71±8</td>
<td>0.907</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.12±0.05</td>
<td>0.29±0.17</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CHF, chronic heart failure; HR, heart rate; CRP, C-reactive protein.
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statistical analyses. A P value <0.05 was considered statistically significant.

Results

Patient Population
Compared with the normal subjects, the patients with DCM tended to be older (63.9±9.9 years vs 58.1±11.5, P=0.087) and have significantly lower diastolic blood pressure (DBP: 69±5 mmHg vs 76±5, P<0.001) and higher serum levels of CRP (0.29±0.17 mg/dl vs 0.12±0.05, P<0.001); however, there were no significant differences between the 2 groups in gender, systolic blood pressure (SBP) or heart rate (HR) (Table 1). The baseline clinical characteristics, biochemistry and concomitant medications in the patients with DCM are summarized in Tables 2 and 3. At baseline, there were no significant differences between the 2 groups with respect to age, gender, blood pressure (BP), HR, NYHA class, biochemistry, including white blood cell count, lipid profiles and plasma CRP levels, echocardiographic findings, including LVEF, or concomitant medications (Tables 2, 3).

Medications
All patients received standard medical treatment, including ACEI or ARB, β-blockers, diuretics, or combinations of these medications, and there were no significant differences between the 2 groups in their medications (Table 2).

Plasma BNP Concentrations
At baseline, there were no significant differences between the Amiodarone and No amiodarone groups in the plasma BNP concentrations (325.3±202.2 vs 388.8±183.7 pg/ml; P=0.472); however, in the Amiodarone group, the plasma BNP concentrations were decreased after 4 weeks of treatment (from 325.3±202.2 to 153.3±161.9 pg/ml; P=0.01), whereas they were unchanged after 4 weeks in the No amiodarone group (from 388.8±183.7 to 392.1±206.8 pg/ml; P=0.749).

Monocyte Cytokine and Chemokine Production by CRP
Our preliminary studies in 4 CHF patients showed that CRP-induced monocyte cytokine and chemokine production was unchanged after 1 or 2 weeks of amiodarone treatment; however, after 4 weeks of amiodarone treatment monocyte cytokine and chemokine production by CRP was significantly reduced (data not shown).

In the present study, 4 weeks of treatment decreased CRP-induced monocyte cytokine and chemokine production in the Amiodarone group (TNF-α: from 167.3±46.4

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Table 2. Baseline Clinical Characteristics of Amiodarone Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone (n=8)</th>
<th>No amiodarone (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.8±11.1</td>
<td>64.5±9.4</td>
<td>0.717</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>6/2</td>
<td>12/3</td>
<td>0.798</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>120±8</td>
<td>114±7</td>
<td>0.109</td>
</tr>
<tr>
<td>Diastolic</td>
<td>66±7</td>
<td>71±4</td>
<td>0.070</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70±10</td>
<td>71±4</td>
<td>0.857</td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4</td>
<td>9</td>
<td>0.646</td>
</tr>
<tr>
<td>III or IV</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Other medications (%)

β-blockers: 87.5 vs 93.3; ACEI: 50.0 vs 53.3; ARB: 62.5 vs 46.7; Diuretics: 100.0 vs 100.0

NYHA, New York Heart Association; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Other abbreviation see in Table 1.

Table 3. Baseline Blood Chemistry and Echocardiography in the Amiodarone Treatment Groups

<table>
<thead>
<tr>
<th></th>
<th>Amiodarone (n=8)</th>
<th>No amiodarone (n=15)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (/μl)</td>
<td>5,613±1,721</td>
<td>6,027±1,293</td>
<td>0.562</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>196±22</td>
<td>185±16</td>
<td>0.220</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>103±35</td>
<td>104±19</td>
<td>0.946</td>
</tr>
<tr>
<td>FPG (mg/dl)</td>
<td>104±27</td>
<td>101±13</td>
<td>0.789</td>
</tr>
<tr>
<td>Serum-Cr (mg/dl)</td>
<td>1.01±0.23</td>
<td>1.14±0.16</td>
<td>0.179</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>325.3±202.2</td>
<td>388.8±183.7</td>
<td>0.472</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.23±0.26</td>
<td>0.32±0.13</td>
<td>0.368</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32.7±6.9</td>
<td>32.1±4.1</td>
<td>0.859</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>47.8±10.7</td>
<td>47.6±3.9</td>
<td>0.970</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>58.8±8.9</td>
<td>58.9±3.7</td>
<td>0.957</td>
</tr>
</tbody>
</table>

WBC, white blood cell; TC, total cholesterol; TG, triglyceride; FPG, fasting plasma glucose; Cr, creatinine; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction; LVDs, left ventricular systolic dimension; LVDd, left ventricular diastolic dimension. Other abbreviation see in Table 1.
to 56.0±22.7 pg·ml⁻¹·10⁻⁶ PBMCs, P=0.012; IL-6: from 2,475.0±777.7 to 937.5±418.2 pg·ml⁻¹·10⁻⁶ PBMCs, P=0.012; MCP-1: from 517.0±133.2 to 128.8±37.5 pg·ml⁻¹·10⁻⁶ PBMCs, P=0.012; IL-8: 7,685.0±2,463.5 to 2,434.6±1,443.5 pg·ml⁻¹·10⁻⁶ PBMCs, P=0.012), but production of these cytokines and chemokines was unchanged in the No amiodarone group (Figure 1). After 4 weeks of treatment, the production of monocyte cytokines and chemokines by CRP in the Amiodarone group were significantly less than that in the No amiodarone group (Figure 1). Cytokine and chemokine production by CRP did not differ between the normal subjects at baseline and the amiodarone groups after 4 weeks of treatment (Figure 1).

BP, HR, Prevalence of VT and Cardiac Function After Amiodarone Treatment

In the Amiodarone group, SBP and HR were comparable at baseline and after 4 weeks of treatment (SBP: 120±8 vs 119±7 mmHg, P=0.197; HR: 70±10 vs 69±8 beats/min, P=0.462). Initial LVEF, LV systolic (LVDs) and LV diastolic (LVDd) diameters were comparable between the Amiodarone and No amiodarone groups (LVEF: 32.7±6.9 vs 32.1±9.1%, P=0.859; LVDs: 47.8±10.7 to 47.6±3.9 mm, P=0.970; LVDd: 58.8±8.9 vs 58.9±4.0 mm, P=0.957). Follow-up echocardiography was performed in all patients. In the Amiodarone group, the LVEF improved significantly from 32.7±6.9 to 39.2±6.9% (P=0.005; Figure 2), the LVDs decreased significantly from 47.8±10.7 to 43.3±11.1 mm (P=0.023), and the LVDd showed a tendency to decrease after 4 weeks of treatment (from 58.8±8.9 to 56.6±7.9 mm; P=0.057). In contrast, in the No amiodarone group the LVEF did not change significantly after 4 weeks (from 32.1±9.1 to 32.2±10.6%, P=0.875; Figure 2) nor did the LVDd (from 58.9±3.7 to 60.1±6.5 mm, P=0.153); however, the LVDs significantly increased after 4 weeks (LVDs;
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from 47.6±3.9 to 49.2±6.0 mm, P=0.027).

We followed all patients with DCM for 1 year in terms of the prevalence of NSVT, using 24-h Holter monitoring at least twice in a year. After 4 weeks of amiodarone treatment, NSVT was not observed in either the Amiodarone or No amiodarone group.

Relationships Between Serum CRP Level, LVEF and Monocyte Cytokine and Chemokine Production by CRP in All Patients at Baseline

In the present study, monocyte MCP-1 production in response to CRP positively correlated with the serum CRP level (r=0.595, P=0.003; Figure 3); however, no correlations were observed between monocyte TNF-α, IL-6 or IL-8 production by CRP and the serum CRP level (TNF-α: r=0.016, P=0.942; IL-6: r=0.365, P=0.087; IL-8: r=0.342, P=0.111, Figure 3). Monocyte IL-6 and MCP-1 production in response to CRP negatively correlated with the LVEF (IL-6: r=–0.489, P=0.018; MCP-1: r=–0.774, P<0.001); however, no correlations were seen between monocyte TNF-α and IL-8 production by CRP and the LVEF (TNF-α: r=–0.303, P=0.161; IL-8: r=–0.381, P=0.073). These data suggest that, in terms of monocyte MCP-1 production at baseline, but not TNF-α, IL-6 and IL-8 production, CRP may be a

Figure 3. Relationship between the serum CRP level and monocyte TNF-α, IL-6, MCP-1 and IL-8 production by CRP. Monocyte MCP-1 production by CRP correlated positively with the serum CRP level, whereas monocyte TNF-α, IL-6 and IL-8 production by CRP did not. Abbreviations see in Figures 1, 2.

Figure 4. Relationships between the changes in LVEF and the changes in monocyte TNF-α (Upper right panel), IL-6 (Upper left panel), MCP-1 (Lower right panel) and IL-8 (Lower left panel) production by CRP at baseline and after 4 weeks of treatment. There was a positive correlation between the changes in LVEF and the changes in monocyte MCP-1 production by CRP, but no correlation between the changes in LVEF and the changes in monocyte TNF-α, IL-6 and IL-8 production by CRP. Abbreviations see in Figures 1, 2.
Relationship Between Changes in LVEF and Monocyte Cytokine and Chemokine Production by CRP at Baseline and After 4 Weeks of Treatment in the Amiodarone Group

There were significant negative correlations between the changes in the LVEF and changes in monocyte MCP-1 production in response to CRP (LVEF: \( r=-0.755, p=0.031 \), Figure 4) at baseline and after 4 weeks of amiodarone treatment; however, no correlations were observed between the changes in the LVEF and changes in monocyte TNF-\( \alpha \), IL-6 and IL-8 production in response to CRP (TNF-\( \alpha \): \( r=-0.311, p=0.453 \); IL-6: \( r=-0.407, p=0.317 \); IL-8: \( r=-0.335, p=0.417 \)). These data suggest that amiodarone may improve cardiac function, at least in part, by decreasing CRP-induced monocyte cytokine and chemokine production, particularly MCP-1.

Discussion

Amiodarone is effective in suppressing life-threatening ventricular tachyarrhythmias and atrial fibrillation\(^5\)\(^-\)\(^20\), and both the GESICA trial\(^4\) and CHF-STAT trial\(^3\) have shown that amiodarone seems to reduce mortality in patients with CHF independently of its antiarrhythmic action.

Monocyte Cytokines and Chemokines in CHF

The pathophysiological mechanisms involved in the deterioration of cardiac function in patients with CHF are complex and complicated; however, overactivation of neurohormonal systems, and the overproduction of biological active molecules including angiotensin II, aldosterone, proinflammatory cytokines and chemokines, may play major roles in the pathogenesis and exacerbation of CHF.\(^3\),\(^4\),\(^21\)

Some experimental studies have shown that transgenic overexpression of TNF-\( \alpha \) and MCP-1 in the myocardium results in myocarditis and the subsequent development of heart failure.\(^22\),\(^23\) TNF-\( \alpha \), IL-6 and MCP-1 enhance free radical generation in myocardial inflammatory cells and promote cardiomyocyte apoptosis in experimental models of CHF.\(^21\),\(^22\),\(^24\),\(^25\) Boyle et al showed that IL-8 neutralization significantly reduced the degree of necrosis in a rabbit model of myocardial ischemia–reperfusion without affecting neutrophil infiltration.\(^26\) These findings suggest that proinflammatory cytokines and chemokines play significant roles in the pathogenesis and development of CHF.

In the present study we demonstrated that production of monocyte cytokines and chemokines in DCM patients was significantly higher than that in normal subjects. The pathophysiological mechanisms underlying this pathway are uncertain and complicated; however, increased release of oxygen species has an unequivocal pathogenetic potential and may also stimulate both inflammatory and thrombotic processes.\(^25\)

CRP in CHF

Anand et al showed that CRP is elevated in CHF and that higher CRP levels are associated with features of more severe heart failure.\(^5\) Interestingly, CRP upregulates the production of macrophage proinflammatory cytokines, such as TNF-\( \alpha \), IL-6 and IL-1\( \beta \), in a dose-dependent manner;\(^6\) induces formation of reactive oxygen species and matrix metalloproteinase expression in monocytes/macrophages;\(^7\) upregulates angiotensin II type 1 receptors in smooth muscle cells, and induces smooth muscle cell proliferation.\(^7\) Therefore, CRP may directly contribute to the pathogenesis and progression of CHF.

In the present study serum levels of CRP correlated well with monocyte MCP-1 production in response to CRP in patients with DCM, thus suggesting that circulating monocytes in vivo may be primed by CRP in terms of MCP-1 production.

Effect of Amiodarone in CHF Patients

An animal study showed that the production of IL-6 was attenuated by the administration of amiodarone to mice with viral myocarditis\(^25\) and amiodarone prevented LV remodeling and improved cardiac function in a rat model of DCM.\(^29\) Matsumori et al has demonstrated in an in vitro study that low concentrations of amiodarone (1 and 10\( \mu \)mol/L) concentrations that are often found in patients with DCM after amiodarone treatment) inhibit production of TNF-\( \alpha \) by human monocytes.\(^3\) On the other hand, Nakajima et al have shown that amiodarone stimulated IL-6 production in cultured human thyrocytes at higher concentrations (10–25\( \mu \)mol/L)\(^3\),\(^8\) Our preliminary in vitro studies showed that amiodarone attenuates the CRP-induced production of monocyte cytokines and chemokines in a dose-dependent manner (from 1 to 10\( \mu \)mol/L)\(^3\),\(^9\) but that higher concentrations of amiodarone (25 and 50\( \mu \)mol/L) significantly upregulate production, probably because of the cytotoxicity of amiodarone for monocytes. Therefore, different concentrations of amiodarone and different cell lines may lead to different results.

Oral et al showed that amiodarone treatment for 2 years increased the TNF-\( \alpha \) level in plasma from CHF patients;\(^33\) however, they did not measure the plasma levels of TNF-\( \alpha \) and monocyte-derived TNF-\( \alpha \) production after 4 weeks of amiodarone treatment nor did they measure monocyte TNF-\( \alpha \) production after 2 years of amiodarone treatment. Therefore, no previous studies have determined the short-term effect of amiodarone treatment on monocyte proinflammatory cytokine and chemokine production in CHF patients in vivo.

The present study demonstrates that short-term amiodarone treatment significantly attenuates CRP-induced monocyte proinflammatory cytokine and chemokine production and thus improves the LVEF in DCM patients with VT. In addition, there was a positive correlation between the changes in LVEF and the changes of monocyte MCP-1 production in response to CRP at baseline and after 4 weeks of amiodarone treatment.

Amiodarone prolongs the action potential duration and refractory period by interfering with potassium transport, and it also has a coronary vasodilator effect through non-comparative blockage of \( \alpha \)- and \( \beta \)-adrenergic receptors. However, in the present study 4 weeks of amiodarone treatment did not significantly affect BP or HR, suggesting that the drug’s beneficial effect on cardiac function might not be related to non-competitive action on the adrenergic receptors.

The recent ATTACH trial has shown the short-term TNF-\( \alpha \) antagonism with infliximab did not improve the clinical condition of patients, and high doses adversely affected those with moderate-to-severe CHF.\(^22\) The precise mechanisms of these results remain to be established. However, the authors speculated that TNF-\( \alpha \) may play an important role in enhancing the production of endogenous vasodilators, including natriuretic peptides and adreno-
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