Clinical Research

Effect of arotinolol on right ventricular function in patients with dilated cardiomyopathy

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Objective Dilated cardiomyopathy (DCM) is generally considered to be accompanied by both left and right ventricular dysfunction, but most studies only analyze the left ventricular function. In this study, we evaluated the effect of arotinolol on right ventricular function in patients with DCM.

Methods Right ventricular ejection fraction (RVEF) and right ventricular diameter (RVD) were measured by two-dimensional echocardiography (2-DE) in 33 DCM patients; RVEF measured by first-pass radionuclide angiography (FPRA) was compared with that by 2-DE. Results The treatment with arotinolol for one year resulted in a reduction in the right ventricular diameter (baseline, 23.0 ± 8.3 mm vs after one-year treatment, 20.7 ± 5.4 mm; P = 0.004) and an associated increase in ejection fraction (baseline, 36.9 ± 10.3% vs after one-year treatment, 45.8 ± 9.6%; P < 0.001); there is a high correlation between the 2-DE method and radionuclide ventriculographic method. The correlation coefficient is 0.933 (P<0.001).

Conclusion Arotinolol therapy could not only improve left ventricular function, but also improve right ventricular function in DCM patients. (J Geriatr Cardiol 2007;4:170-173.)

Key Words dilated cardiomyopathy; arotinolol; right ventricular function

Dilated cardiomyopathy (DCM) is generally considered to be accompanied by both left and right ventricular dysfunction, but in most studies only the left ventricle (LV) function has been analyzed, with less attention paid to right ventricle (RV) function.1-3 However the RV ejection fraction (RVEF) is related to the capacity for exercise tolerance and to the prognosis in DCM patients with severe LV failure; therefore it is necessary to evaluate RV function in such patients.

The beneficial effect of β-blocker therapy in DCM patients with chronic congestive heart failure (CHF) has been confirmed in many studies.4-6 Arotinolol is an alpha- and beta-blocker without antioxidant properties and the ratio of alpha to beta is similar to carvedilol (alpha:beta = 1:8). Our goal in the present study is to evaluate the effect of arotinolol on right ventricular function in patients with DCM.

Methods

Inclusion criteria

Inpatients and outpatients aged 18 to 65 years old with established DCM and CHF were enrolled in the study, which consisted of 33 patients with 24 males and 9 females. Their left ventricular ejection fraction (LVEF) <40%; LV end-diastole diameter (LVEDd) > 60 mm; and with stable hemodynamics. Patients with the following conditions including hypersensitivity to β-blocker, coronary heart disease, chronic alcohol intoxication, hypertension, valvular heart diseases, hypertrophic cardiomyopathy, restrictive cardiomyopathy, severe arrhythmia, diabetes mellitus, severe lung diseases, and congenital heart diseases were excluded from the study.

The protocol was approved by the ethics committee of the hospital and was carried out in accordance with the guidelines of Good Clinical Practice of Ministry of Health of China. All patients gave their informed consent before entering the study.

Study protocol

All enrolled patients had two periods of treatment. During the first period patients received the routine medication for CHF including digoxin, diuretics and angiotension converting enzymes inhibitor (ACEI) for a week, and then completed all examinations required for baseline observation; the second period lasted 12 months during which time all patients were given arotinolol 1.25 mg twice daily for 1 or 2 weeks. The dose was increased every 1 to 2 weeks until the maximal tolerant dose. Dose titration was deferred or the dose was lowered if the patients could not tolerate the initial dosage or the systolic blood pressure decreased to less than 90 mmHg after adjusting the dosage of diuretics or other drugs.
After treatment  
63.08 ±8.39*  
50.89 ±8.17*  
2.83 ±0.67#  
41.13 ±9.45*  
20.7 ±5.4#  
45.8 ±9.6*  

Table 1. Changes in variables for both LV and RV function before and after arotinolol treatment (±s)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter of left ventricle and systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDd (mm)</td>
<td>69.90 ±9.14</td>
<td>63.08 ±8.39*</td>
</tr>
<tr>
<td>LVESd (mm)</td>
<td>59.52 ±8.83</td>
<td>50.89 ±8.17*</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>2.54 ±0.78</td>
<td>2.83 ±0.67#</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>27.39 ±7.94</td>
<td>41.13 ±9.45*</td>
</tr>
<tr>
<td>Diameter of right ventricle and systolic function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>23.0 ±8.3</td>
<td>20.7 ±5.4#</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>36.9 ±10.3</td>
<td>45.8 ±9.6*</td>
</tr>
</tbody>
</table>

Table 2. The correlation analysis between the RVEF measured by 2-DE and by FPRA (n=24)

<table>
<thead>
<tr>
<th>Method</th>
<th>t±s</th>
<th>Regression equation</th>
<th>Correlation coefficient</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-DE Method(RVEF1)</td>
<td>36.8 ±8.6</td>
<td>RVEF2=-2.182+1.003RVEF1</td>
<td>0.933</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FPRA Method(RVEF2)</td>
<td>34.7 ±9.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Methods

Echocardiographic study

M-mode and 2-dimensional echocardiographic studies were performed with an ACUSON 128 type electronic phase array echo imaging system equipped with a 3.5-MHz transducer; the four-chamber view was shown by 2-DE with clear demonstration of mitral valve and tricuspid valve. End diastole and end systole were determined by electrocardiographic trigger with end diastole on the top of QRS complex and end systole at the end of T wave. The images of end diastole and end systole were recorded, then the ventricular outline was traced by hand and digitized with cursor; the long axis diameter of left ventricle was defined as the distance from the midpoint of mitral annulus to apex and the long axis diameter of right ventricle was defined as the distance from the midpoint of tricuspid annulus to apex. The volumes at end diastole and end systole for both left and right ventricles and then the RVEF and LVEF were calculated with single plane Simpson professional software. The diameters of both left and right ventricles and ventricular wall thickness were measured by M-mode echocardiography. Data from three cardiac cycles were analyzed and then a mean value for each cycle was acquired.

RVEF measured by FPRA

The RVEF was also measured by first past radionuclide angiography (FPRA) on the day of 2-dimensional echocardiographic measurement of RVF with the Toshiba 90B SPECT â-Camera Data Collection and Analysis system. All patients underwent right ventriculography at 30° in the left anterior oblique view with a bolus infusion of 99mTc-RBC 740MBq; when contrast medium first passes the cardiac chamber, dynamic imaging was performed at a rate of 32 frames per second, and then the imaging data were read into the computer for processing. The frames from three cardiac cycles were analyzed and a mean value for each cycle was acquired.

Statistical analysis

All calculations were performed on a personal computer with the statistical package SPSS 11.5. Data are presented as mean ± SD. Changes in variables for both left and right ventricular function after arotinolol treatment were analyzed using Student’s paired t-test, and the relationship between RVEF measured by 2-DE and by FPRA was analyzed with logistic regression analysis; a value of P<0.05 was considered significant.

Results

Changes in both left and right ventricular function after arotinolol treatment

Changes in both left and right ventricular function after 12-month treatment with arotinolol (see Table 1) showed that the LV systolic function in patients with DCM was significantly improved after 12 month treatment with arotinolol; LVEF increased from 27.39 ± 7.94% to 41.13 ± 9.45% (P<0.01), while RVD was markedly reduced from 23.0 ± 8.3mm to 20.7 ± 5.4 mm (P<0.01) and RVEF was significantly increased from 36.9 ± 10.3% to 45.8 ± 9.6% (P<0.001).

Correlation analysis between the RVEF measured by 2-DE and by FPRA

Out of a total of 33 patients enrolled, data from 24
patients has been integrated (Table 2). In Table 2, correlation analysis shows that two methods of RVEF measurement (by 2-DE and by FPRA) were well correlated with a linear regression, correlation equation:

\[ RVEF_2 = -2.182 + 1.003 \times RVEF_1; \text{the correlation coefficient } r = 0.933 (P<0.001). \]

The corresponding plot seen in figure 1.

**Analysis of adverse events**

None of these patients withdrew from the study prematurely because of laboratory abnormality or adverse events. The most frequently repeated adverse event was nausea, as experienced by 8 patients; and 3 patients experienced dizziness.

**Discussion**

The quantitative analysis of cardiac function generally focuses on the LV function. While the LV function may be accurately assessed at standard Doppler echocardiography, the evaluation of the RV structure and function has several limitations due to a difficult approach, mainly related to the fact that this chamber is located behind the sternum as well as its geometric configuration. It is now recognized that the RV is not a passive conduit, but functions as a pump may directly affect the function of the circulatory system.

The radionuclide ventriculography is a well-known, non-invasive method for RV evaluation with its precision most proximate to that of the RV X-ray angiography, which is often used as a standard method for comparison studies.\(^1,7,8\) The 2-DE method and the radionuclide ventriculographic method show a high correlation between the 2-DE method and the radionuclide ventriculographic method with its regression equation of \(RVEF_2 = -2.182 + 1.003 \times RVEF_1\) and correlation coefficient \(r = 0.933 (P<0.001)\). Therefore the 2-DE Simpson method can accurately measure the RVEF and thus is a reliable method to evaluate the RV function.

Arotinolol is a competitive antagonist at both \(\alpha\)- and \(\beta\)-adrenoceptors and the ratio of alpha to beta receptors is similar to that of carvedilol (alpha:beta = 1:8).\(^9\) Arotinolol reaches a peak concentration at two hours after dosing and has a half life of 11.2 hours. In previous studies, it was found that arotinolol may improve the balance between the sympathetic and parasympathetic nervous systems. Morimoto et al.\(^13\) found that the potent blocking effects of arotinolol and its metabolite on the increased renin release in response to \(\beta\)-adrenoceptor stimulation may contribute to the effect of this agent. These blocking effects inhibited isopropanol-induced enhancement of renin release in a concentration-dependent manner. Similar results were observed with propranolol or labetalol, although the inhibitory potencies of these agents were considerably lower than that of arotinolol.

The results of this study showed that both LVEF and RVEF were significantly increased and the RVD was significantly decreased after treatment with arotinolol. The study indicates that arotinolol has a significant effect in the treatment of both left and right ventricular dysfunction in patients with DCM. The mechanism of benefit is unclear, but it may be in all likelihood associated with its \(\beta\)-blocking effects on the neurohormonal system and sympathetic nervous system.

The study also has its limitations; researchers were not blinded to treatment, but measurements of observed parameters were performed in a blinded manner. Another limitation is the small number of study patients. We are aware that a large number of subjects would have improved the reliability of our results.

In conclusion, arotinolol for twelve months treatment has a favorable effect on improvement of both left and right ventricular function in patients with IDCM and is generally safe and well tolerated. The mechanism of action of arotinolol and the long-term benefits of this agent in the management of CHF in patients with DCM should be elucidated by large-scale outcome studies.

**References**


