Effects of Bisoprolol and Carvedilol on Left Ventricular Remodeling in Patients with Chronic Heart Failure

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Abstract

The purpose of the present research was to study the types of left ventricular (LV) remodeling in post-MI patients with chronic heart failure (CHF) and assess the impact of bisoprolol and carvedilol on LV remodeling.

Material and Methods: The study included 217 post-MI patients with CHF between the ages of 38 and 60 (mean age 50.6±6.8 yrs) who were treated at the cardiology department of Tashkent Medical Academy. NYHA functional class (FC) of CHF was determined by the 6-minute walk test (6MWT). All the patients were divided into two groups. Group 1 consisted of 107 post-MI patients with FC I-III, who received bisoprolol on the background of basic therapy during 6 months; Group 2 consisted of 110 post-MI patients with FC I-III, who received carvedilol on the background of basic therapy during 6 months. The mean daily dose of bisoprolol was 10 mg, and carvedilol 25-50 mg. All patients underwent clinical examination, ECG, and echocardiography.

Result: Reverse remodeling and improvement in left ventricular function was observed in both groups, with a slight advantage in the bisoprolol group. There was a decrease in the number of patients with prognostically unfavorable types of remodeling (eccentric and concentric LVH) and restoration of normal LV geometry.

Keywords: chronic heart failure; left ventricular remodeling, bisoprolol; carvedilol.

Introduction

Chronic heart failure (CHF) is still the most common, severe and prognostically unfavorable outcome of many diseases of the cardiovascular system [1]. The outcome of CHF remains very serious regardless of its etiology [2-4]. In post-MI patients, according to the Framingham study, CHF developed within 5 years, and the risk of its development in patients with left ventricular (LV) dilatation was significantly higher than in patients with normal LV cavity size [5]. A combination of the lesions with early and late mechanical and neurohormonal effects contribute to the LV restructuring and the post-MI remodeling in post-MI patients. In post-MI patients, the LV remodeling process is caused by the death of a large number of cardiomyocytes and continues after the cessation of the damaging effect of ischemia. The loss of part of a functioning myocardium is accompanied by a complex of structural changes involving both the damaged and undamaged areas of the myocardium. This process is adaptive in its nature, aimed at maintaining a normal cardiac output and adequate myocardial stress. These changes in the structure and geometry of the heart chambers, referred to as “adaptive remodeling of the heart,” often precede the clinical manifestations of heart failure. However, it is known that heart failure develops in the future in a significant proportion of post-MI patients. The cause of this complication is that the remodeling process becomes maladaptive in character with progressive dilatation of the LV, an alteration of its geometry, and final fall of the pumping function [6-8].

Use of beta-blockers opened a new era in treatment of CHF patients [9,10]. Many studies, including long-term multicenter studies, determined that this drug group has a positive impact on the clinical course, the quality of life,
and the prognosis of post-MI patients and patients with heart failure [11,12]. Despite numerous clinical and experimental studies on the remodeling processes, questions about the timing and types of LV remodeling in patients with different functional classes remain a matter of debate. Data on the close relationship between the episodes of myocardial ischemia and impaired myocardial relaxation, which is one of the most important pathogenetic mechanisms of diastolic dysfunction and LV remodeling, are the subject of special attention. The purpose of our work was to study the types of LV remodeling in post-MI patients with CHF and assess the impact of bisoprolol and carvedilol on LV remodeling.

**Materials and Methods**

The study included 217 post-MI patients with CHF between the ages of 38 and 60 (mean age 50.6±6.8 yrs), who were treated at the cardiology department of Tashkent Medical Academy. NYHA functional class (FC) of CHF was determined by the 6-minute walk test (6MWT) and the Russian scale of evaluation of the clinical condition of the patients (V.Yu. Mareev, 2000). All the patients were divided into two groups. Group 1 consisted of 107 post-MI patients with FC I-III, who received bisoprolol, β1-selective beta-blocker, on the background of basic therapy during 6 months; Group 2 consisted of 110 post-MI patients with FC I-III, who received carvedilol, nonselective beta-blocker with α1-, β1- and β2-blocking properties, on the background of basic therapy during 6 months. The mean daily dose of bisoprolol given to Group 1 patients was 10 mg; the mean daily dose of carvedilol in Group 2 patients ranged from 25 to 50 mg.

The standard therapy includes spironolactone, ACE inhibitors, antiplatelet agents. The control group comprised 20 healthy, age-matched, randomly selected male persons. Exclusion criteria were diabetes, atrial fibrillation, COPD, asthma, and acute stroke. Echocardiography was performed using the ultrasound system Toshiba SSH – YO(60)A (Japan). Standard views and techniques in M- and B- modes were used according to guidelines of the American Society of Echocardiography [13]. Measurement of end-diastolic and end-systolic LV volumes (EDV and ESV of LV) was carried out using the modified Simpson’s method in the apical 2-wire and 4-chamber view. Left ventricular dimension and left ventricular relative wall thickness (LVRWT) were measured by echocardiography in M-mode according to the recommendations of the American Society of Echocardiography [14]. Then, using the standard formula, stroke volume (SV) and left ventricular ejection fraction (LVEF) were calculated. LV mass and LVMi (LV mass standardized by body surface area) were measured by M-mode echocardiography with the use of the Devereux formula [15,16]. Finally, end-diastolic and end-systolic sphericity index (EDSI and ESSI), as well as meridional end-systolic wall stress (mESS) were measured. LV diastolic function was evaluated by pulsed Doppler echocardiography. Maximum velocities $E$ and $A$, $E/A$, and the isovolumic relaxation time (IVRT) were measured.

The study was approved by the Republican Specialized Scientific - Practical Medical Centre of Therapy and Medical Rehabilitation. Written informed consent was obtained from each patient.

Statistical analysis was performed using ECXEL 6.0 for Windows-95. For data with normal distribution, inter-group comparisons were performed using Student’s *t*-test. The mean (M) and standard deviation (SD) were calculated. A probability value of $P<0.05$ was considered statistically significant.

**Results**

In patients with CHF FC-I, normal values of LVEF were revealed. By increasing the degree of CHF, LVEF progressively decrease, so in patients with FC-II, LVEF was 20.1% ($P<0.001$) less than in patients with FC-I; furthermore, EDV and ESV were also slightly higher than in patients with FC-I. Despite the increase in intramyocardial tension and dilation of the heart chambers, stroke volume was within normal values. With an increase in CHF FC, LVMI and wall thickness tended to increase, but without statistical significance. In patients with FC-II, mESS was higher by 26.9% ($P<0.01$) than in patients with FC-I; this was probably due to the increase in LV intramyocardial tension. EDSI and ESSI had a tendency to increase in patients with FC-II. Development of CHF FC-III was accompanied by even more pronounced structural changes of LV. In patients with CF-III compared to patients with FC-I, EDD, EDV, and ESD were 16.6% ($P<0.001$), 37.9% ($P<0.001$), and 36.8% ($P<0.001$) greater, respectively, and ESV increased more than 2-fold. Myocardial contractility was characterized by a decrease in LVEF by 37.2% ($P<0.001$) compared to the control group. Also noted was an increase in the longitudinal dimensions in diastole by 1.3% in patients with CHF FC-I. These changes were accompanied by an increase in EDSI and ESSI by 11.7% and 15.9% ($P<0.001$), respectively. An increase in intramyocardial tension in systole by 5.1%, compared to the level in the end-systolic period, was characterized by a significant increase in mESS by 38.1% ($P<0.02$) compared to that in patients with CHF FC-I.

Pathological changes in LV myocardium after MI resulted in the development of the spherical LV shape. LV remodeling in post-MI patients is accompanied with changes of muscle mass; there is LV dilatation with increases in EDD and ESD. Wall thickening in the intact myocardium without changes in LV geometry and LVMi occurred in 15% of patients, which corresponded to the presence of concentric left ventricular remodeling (CLVR). Concentric left ventricular hypertrophy (CLVH) was observed in 52%, and signs of eccentric left ventricular hypertrophy (ELVH) were observed in 33% of patients.

CLVH was found in 21.3% of patients with FC-I and in 50.8% of patients with FC-II. ELVH was found in 58.3% of patients with FC-III. A diastolic variant of heart failure occurred in 76.4% of patients with CLVR and 82% of patients with CLVH, and only in 43.6% of patients with ELVH. In ELVH, systolic and mixed variants of heart failure occurred equally often (48.6 and 45.9%, respectively).

In patients with CLVH, LVEF was not significantly decreased; at the same time, $E$ decreased by 27.7% ($P<0.05$) and $A$ by 17.4% ($P<0.05$) compared to the control group. In
patients with ELVH, E decreased by 37.0% (P<0.05), A by 12.5% (P<0.05), and LVEF by 40.8% compared to the control group. In patients with CLVR, E decreased by 26.0% (P<0.05), A by 18.7% (P<0.05), and LVEF by 21.4% compared to the control group (Table 1).

Table 1.
Types of LV remodeling and parameters of LV systolic and diastolic function

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control group</th>
<th>CLVR</th>
<th>CLVH</th>
<th>ELVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>E, cm/sec</td>
<td>75.9±9.8</td>
<td>56.2±11.1*</td>
<td>54.9±13.8*</td>
<td>47.8±14.9*</td>
</tr>
<tr>
<td>A, cm/sec</td>
<td>63.1±11.4</td>
<td>51.3±12.5*</td>
<td>52.1±12.9*</td>
<td>55.2±11.9*</td>
</tr>
<tr>
<td>E/A</td>
<td>1.2±0.18</td>
<td>1.10±0.14*</td>
<td>1.05±0.17*</td>
<td>0.87±0.12</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>66.8±8.8</td>
<td>56.0±15.2*</td>
<td>57.8±13.1*</td>
<td>44.4±13.5*</td>
</tr>
<tr>
<td>LVRWT</td>
<td>0.42±0.05</td>
<td>0.46±0.026*</td>
<td>0.48±0.023*0</td>
<td>0.34±0.018*</td>
</tr>
</tbody>
</table>

* P<0.05 vs control group

Our results showed that diastolic heart failure, an isolated systolic variant, and a mixed variant of heart failure occurred in 63.3%, 3.8%, and 32.9% of cases, respectively, in post-MI patients with CHF FC I-III. The maximum decrease in diastolic relaxation occurred in patients with ELVH, which was accompanied by the most significant decrease in LVEF. In patients with CLVH and CLVR, LV diastolic filling was reduced while velocity of circumferential fiber shortening was maintained and, as a consequence, LVEF at rest was reduced.

Analysis of the dynamics of the LV geometric parameters during long-term therapy with bisoprolol and carvedilol revealed the characteristic features for the observed groups. In post-MI patients with FC-I after 6 months’ therapy with bisoprolol and carvedilol, we found a significant decrease in EDD by 9% and 12.2% (P<0.001), EDV by 18.9% and 26% (P<0.01), ESD by 11.1% and 17.5% (P<0.001), and ESV by 30.1% and 36.3% (P<0.005), respectively, compared to baseline data. Although baseline LVEF was within normal values in these patients, by the end of treatment this parameter had significantly increased by 12% for bisoprolol and 14.5% (P<0.001) for carvedilol. In post-MI patients with FC-II after 6 months’ therapy with bisoprolol and carvedilol, we observed a significant decrease in EDD by 9% and 10.5% (P<0.001), respectively, and in ESD by 7% and 15.9% (P<0.001), respectively. These decreases were accompanied by an increase in LVEF by 11.8% and 14.8%, respectively.

In post-MI patients with FC-III after 6 months’ therapy with bisoprolol, we found a significant decrease in EDD and ESD by 11.1% and 15.4% (P<0.001), EDV and ESV by 26.2% and 35.8% (P<0.001), respectively, compared to baseline data. These decreases were accompanied by an increase in LVEF by 17.3%.

Therapy with bisoprolol and carvedilol for 6 months had a positive impact on LV remodeling. In the group receiving carvedilol, a statistically significant decrease in LVMI was noted, improving LV systolic function, which resulted in a significant increase in LVEF in patients with ELVH. The type of cardiac remodeling had also undergone significant changes: at baseline, CLVH was predominant (52.3%), and ELVH accounted for 35%. At the end of observation, we noted a decrease in the proportion of patients with CLVT and ELVH; normal LV geometry was determined in 40.1% of patients. By the end of the observation in patients with baseline CLVH (n=56), CLVR and normal LV geometry was observed in 16 patients, ELVH in 4 patients, and CLVH in 36 patients; in patients with baseline ELVH (n=38), CLVR and normal LV geometry was observed in 10 patients, CLVH in 4 patients, and ELVH in 24 patients.

In the group receiving carvedilol, it was also noted a decrease in LVMI and statistically significant increase in LVEF in patients with ELVH. The type of cardiac remodeling had also undergone significant changes: at baseline, CLVH was predominant (55%), and ELVH accounted for 33.6%. At the end of observation, we noted a decrease in the proportion of patients with CLVT and ELVH; normal LV geometry was determined in 33.1% of patients. By the end of the observation in patients with baseline CLVH (n=61), CLVR and normal LV geometry was observed in 10 patients, ELVH in 8 patients, and CLVH in 43 patients; in patients with baseline ELVH (n=37), CLVR and CLVH was observed in 8 patients and ELVH in 29 patients.

Conclusion

Thus, reverse remodeling and improvement in left ventricular systolic function was observed in both groups, with a slight advantage in the bisoprolol group. There was a decrease in the number of patients with prognostically unfavorable types of remodeling (eccentric and concentric LVH) and restoration of normal LV geometry.

Competing interests

The authors declare that they have no competing interests.

References


