

Effect of Carvedilol on Beta-Adrenoceptor Density and Adenylate Cyclase Activity in Erythrocyte Membranes of post-MI Patients with Chronic Heart Failure

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Abstract

The purpose of this study was to evaluate the effect of carvedilol on β_2 -adrenoceptor density and AC activity in erythrocyte membranes of post-MI patients with CHF (NYHA FC I-III). The study included 56 post-MI male patients aged from 45 to 55 years (mean age 51.2 ± 4.6) with CHF FCII-III. All the patients were divided into two groups according to the New York Heart Classification (NYHA) functional class (FC). Group 1 consisted of 30 post-MI patients with CHF FC-II and Group 2 consisted of 26 post-MI patients with CHF-III. The β_2 -adrenoceptor density in erythrocyte membranes was determined using β -APM-AGAT kits. The adenylyl cyclase activity in red blood cells homogenate was determined according to the method of Y. Salomon (1979). All patients received carvedilol on the background of basic therapy.

In post-MI patients with CHF FC I-III, the increased β_2 -adrenoceptor density was accompanied by desensitization of the adenylate cyclase system, which was more pronounced in patients of Group 2. Long-term therapy with carvedilol reduced the β_2 -adrenoceptor density and increased the adenylate cyclase activity in erythrocyte membranes of post-MI patients with CHF FC II-III.

Keywords: post-MI patients; chronic heart failure; β_2 -adrenoceptor density; adenylate cyclase activity; carvedilol.

Introduction

Among cardiovascular diseases, chronic heart failure (CHF) is one of those the frequency of which is constantly increasing. Myocardial infarction (MI) is one of the main causes of HF as a result of an ischemic injury coupled with early and late mechanical and neurohormonal effects, contributing to the development of left ventricular (LV) remodeling [1,2]. In the early stages of LV dysfunction, activation of several neurohormonal systems (sympathetic-adrenal system, the renin-angiotensin-aldosterone system, the natriuretic peptide system, and several others) and mediators, including cytokines and endothelins, was noted in a series of multicenter studies. The adenylyl cyclase (AC) system also plays a key role in the heart's adaptation through a series of biochemical reactions.

This system mediates the damage effects of catecholamines through changes in the sensitivity of cardiomyocytes to beta-adrenergic stimulation due to low concentration of β_1 -adrenergic receptors on the outer membrane. Normally, the stimulation of β_1 - and β_2 - adrenoceptors by catecholamines modifies the AC activity in cardiomyocytes. During long sympathetic hyperactivation, disturbances occur in the β -adrenergic receptors, which are characterized by a decrease in the number and density of the cardiomyocyte β_1 -adrenoceptors [3,4]. It should be noted that the idea of neurohormonal inhibition has taken a leading role in the pathogenetic therapy of CHF in recent decades. It is known that the positive effect of β -blockers (BB) on myocardial function is associated with the negative chronotropic and inotropic effects that result in a decrease in the energy requirements of the myocardium. In addition, BBs protect the myocardium from the toxic effects of catecholamines, improve its metabolism, and possess antiarrhythmic and vasodilating effects [5,6].

The purpose of this study was to evaluate the effect of carvedilol on β_2 -adrenoceptor density and the AC activity in

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erythrocyte membranes of post-MI patients with CHF (NYHA FC I-III).

Materials and Methods

The study included 56 post-MI male patients aged from 45 to 55 (mean age 51.2 ± 4.6 yrs) years with CHF FCII-III; duration of post-MI period was 2.3 ± 0.9 years. Written informed consent was obtained from patients and their parents. All the patients were divided into two groups according to the New York Heart Classification (NYHA) functional class (FC). NYHA FC 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 patients underwent clinical examination, ECG, and echocardiography. Group 1 consisted of 30 post-MI patients with CHF FC-II and Group 2 consisted of 26 post-MI patients with CHF-III.

The β_2 -adrenoceptor density in erythrocyte membranes was determined using β -APM-AGAT kits. The AC activity in red blood cells homogenate was determined according to the method of Y. Salomon [7].

All patients received a carvedilol, nonselective beta blocker with α_1 -, β_1 - and β_2 - blocking properties, on the background of basic therapy (ACE inhibitors, spironolactone, nitrates, aspirin, loop diuretics). Initial carvedilol dosage was 3.125 mg and was titrated to achieve the target dosage of 25–50 mg twice a day. Mean carvedilol dosage was 23.8 ± 4.6 mg/day in Group 1 and 33.65 ± 6.9 mg/day in Group II. Exclusion criteria were diabetes, heart rhythm disorders, COPD, asthma, and acute stroke.

Results were statistically processed using the *software* package Statistica 6.1 for Windows and the Excel package of Microsoft Excel 2007. The mean (M) and Standard Deviation (SD) were deduced. For data with normal distribution, intergroup comparisons were performed using Student's *t*-test and *F*-test. The mean (M) and standard error of the mean (m) were calculated. Pearson's Correlation Coefficient (*r*) was used to determine the strength of the relationship between the two continuous variables. Spearman's rank correlation coefficient was also used. A probability value of $P < 0.05$ was considered statistically significant.

Results and Discussion

In Group 1 patients, the initial erythrocyte β_2 -adrenoceptor density was 27.7 ± 1.4 CU and exceeded the control value group by 2.4 times; in Group 2 patients it was 30.8 ± 1.3 CU and exceeded the control value by 2.9 times. Revealed disturbances were linked to the altered activity of AC, which activity is regulated by the extracellular and intracellular mediators. The increased β_2 -adrenoceptor density was accompanied by desensitization of the AC system [8], which was more pronounced in patients of Group 2. Basal AC activity was less by 31.9% in patients of Group 1 compared to the control group (4.15 ± 0.14 vs 6.1 ± 0.19 pmol/mg/min); in patients of Group 2 it was less by 41.6% compared to the control group (3.56 ± 0.13 vs 6.1 ± 0.19 pmol/mg/min) and by 14.2% compared to Group 1 patients.

Correlation analysis revealed an inverse correlation between the erythrocyte β_2 -adrenoceptor density and AC activity ($r = -0.54$, $P < 0.05$). The functional state of the beta-adrenergic receptors is determined by the membrane AC activity, which is activated by the epinephrine- β -adrenergic receptor complex and many extracellular and intracellular regulators [9-12]. In the control group, we found an increase in the epinephrine-stimulated AC activity of about 2 times in comparison with basal level (11.3 ± 0.5 vs 6.1 ± 0.19 pmol/mg/min, $P < 0.01$).

In Group 1 patients, the epinephrine-stimulated AC activity was lower about 2 times compared to the control group (5.5 ± 0.19 pmol/mg/min vs 11.3 ± 0.5 pmol/mg/min). In Group 2 patients, this parameter was reduced to 3.85 ± 0.19 pmol/mg/min and was 65.9% ($P < 0.05$) lower than in the control group and 28.7% lower than in Group 1 patients.

A significant increase in the epinephrine-stimulated AC activity of erythrocyte membranes in healthy controls by 85% reflects an adequate response of the membrane AC to stimulation. Revealed disturbances in the epinephrine-stimulated AC activity in post-MI patients with CHF reflect the desensitization of the erythrocyte AC system, which is exacerbated by severity of the CHF.

Our study has shown that therapy with carvedilol for 6 months led to a decrease of β_2 -adrenoceptor density by 15.7% ($P < 0.05$) in post-MI patients with CHF FC-II and by 22.7% ($P < 0.05$) in post-MI patients with CHF FC-III in comparison with the initial levels. A decrease of β_2 -adrenoceptor density during therapy with carvedilol was accompanied by an increase in AC activity by 15.3% in patients with CHF FC-II and 13.9% in patients with CHF FC-III in comparison with the initial data ($P < 0.05$). Long-term therapy with carvedilol reduced the β_2 -adrenoceptor density and increased the AC activity in erythrocyte membranes of post-Mi patients with CHF FCII-III.

In conclusion, in post-MI patients with CHF FC I-III, the increased β_2 -adrenoceptor density is accompanied by desensitization of the adenylate cyclase system, which is more pronounced in patients of Group 2. Long-term therapy with carvedilol reduces the β_2 -adrenoceptor density and increases the AC activity in erythrocyte membranes of post-Mi patients with CHF FCII-III.

Competing interests

The authors declare that they have no competing interests.

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