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Xroniki ürək çatışmazlığı olan xəstələrdə karvedilolun qanın hemoreoloji, hemokoaqulyasiya və lipid metabolizmi göstəricilərinə təsiri.

U.G.Zakiyeva[1], T.Sh. Jahangirov[1]

Aim. We studied the influence of Carvedilol on the indices hemorheology (erythrocyte deformability, fibrinogen, and hematocrit) and the hemocoagulation state (blood fibrinolitic activity, plasma recalcification time, protrombin index, and spontaneous aggregation of thrombocytes), plasma malondialdehyde in patients (pts) with chronic heart failure (CHF).
Material and methods. 30 pts with NYHA class II or III CHF after myocardial infarction [age 45 to 71 years] were treated with basic therapy (glycosides+ diuretics+ ACE inhibitor) and Carvedilol was added from 3,125 - 6, 25 mg twice a day to 12,5 - 25 mg (twice) for 12 weeks (3 months).
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Results. Before addition of Carvedilol we discovered the significant increase of fibrinigen by 20% and hematocrit by 7,6%; reduction of erythrocyte deformability by 14,5%; completely depressed blood fibrinilotic activity, decrease of plasma recalcification time by 40%; increase of protrombin index by 19%; speeding-up of spontaneous aggregation of thrombocytes, increase of plasma malondialdehyde by 10,7% in pts with CHF. After 12 weeks (3 months) of treatment with Carvedilol the indices were changed: the fibrinogen was decreased by 40% and the hematocrit decreased by 16,1%; the erythrocyte deformability increased by

Yazışma üçün əlaqə:
U.G.Zakiyeva[1], T.Sh. Jahangirov[1]
1 National Cardiac Society of Azerbaijan,SRİ of Cardiology,after named J. Abdullayev
Ulviyaz@yahoo.com;
drjahanqirov@yahoo.com

24,5%; the blood fibrinolytic activity increased by 50%; the plasma recalcification time increased by 50%; the protrombin index decreased by 33%; decreased the spontaneous aggregation of thrombocytes and plasma malondialdehyde by 8,9% decreased in pts with CHF (0.05 > Pu < 0.01).

Conclusion. The addition of Carvedilol "above" basic therapy promoted a pronounced improvement of hemorheology, hemocoagulation state and lipid metabolism, which resulted in reduction of heart failure degree and improvement of the remote prognosis.

Summary. Chronic heart failure (CHF) is accompanied by hemorheology, hemocoagulation and lipid metabolism disturbances; the most important of those are the following: increase of fibrinogen level, decrease of erythrocyte deformability and increase of aggregative properties of blood cells, increase of plasma malondialdehyde.

Key words: chronic heart failure, carvedilol, hemorheology, hemocoagulation and lipid metabolism

Açar sözlər: xroniki ürək çatışmazlığı, karvedilol, hemoreologiya, hemokoaqulyasiya, lipid metabolizmi

Məqsəd. Xroniki ürək çatışmazlıqlı (XÜÇ) olan xəstələrdə, qanın hemoreoloji (eritrosit deformabilliyi, fibrinoqen və hem atokrit) və hemokoaqulyasiya vəziyyəti (qanın fibrinolitik fəaliyyəti, plazma rekalsifikasiya vaxtı, protrombin indeksi, və trombositlərin spontan aqreqasiyası) və plazma malondialdehiti göstəricilərinin Karvedilolun təsiri altında dəyişməsini tədqiq etməkdir.

Material və metodlar. Postinfarkt kardiosklerozlu, XÜÇ-lı, NYHA sinif II və ya III olan xəstələrdə [45 -71 yaş arasında]12 həftə (3 ay) müddətində əsas terapiya (ürək qlikozidləri+diuretiklər+AÇF inhibitorları) ilə yanaşı, Karvedilol titrləmiə üsulu ilə, 3,125 mg-dan başlayaraq, 6,25,12,5-25 mg-dək, gündə iki dəfə verilib. Eyni zamanda, qanda hemoreoloji, hemokoaqulyasiya və lipidlərin peroksidləşmıə göstəricisi olan plazma malondialdehiti öyrənilib.

Nəticələr. Karvedilol əlavə edilməmışdən əvvəl, əsas terapiya fonunda müvafiq olaraq hematokrit və fibrinoqen 7,6% və 20% artmış; eritrositlərin deformabilliyi 14,5% azalmış; qanın fibrinolitik fəalliyəti,plazmanın rekalsifikasiya vaxtı 40% azalmış; protrombin indeksi 19% artmış; trombositlərin spontan aqreqasiyası sürətlənmiş və XÜÇ olan xəstələrdə plazmada olam malondialdehitlərin miqdarı 10,7% artmışdır. Karvedilolla 12 həftəlik (3 ay) müalicədən sonra indekslər aşağıdakı şəkildə dəyişilmişdir: fibrinoqen 40%, hematokrit isə 16,1% azalmışdır; eritrositlərin deformabilliyi 24,5% artmışdır; qanın fibrinolitik fəaliyyəti 50% artıb; trombositlərin spontan aqreqasiyası və plazma malondialdehitləri 8,9% azalmış; plazmanın rekalsifikasiya vaxtı 50% artmışdır; protrombin indeksi 33% azalmışdır (0.05 > Pu < 0.01).

Yekun. Postinfarkt kardiosklerozlu, XÜÇ-lı xəstələrdə, Karvedilol əsas terapiyaya əlavə edildikdə, qanın hemoreoloji, hemokoaqulyasiya vəziyyəti yaxşılaşır və lipid mübadiləsi təkmilləşir, ürək çatışmazlığı dərəcəsi azalır və gələcək proqnoz yaxşılaşır.

INTRODUCTION

Despite improvements in the management of cardiovascular risk factors and disease over the last 50 years that have led to a reduction in mortality from myocardial infarction and stroke, hospital admissions with heart failure have risen unabated (1). The data of experimental and clinical studies testifying the important role of rheological indices of blood in formation of the heart failure were published a lot of years ago (2). Clinically, lipid peroxidation is revealed by an increase of malondialdehyde (MDA): high serum concentrations of MDA in patients with myocardial infarction are indirect evidence of oxygen free radicals toxicity in

these conditions (3,4). Oxidative stress is also involved in the induction of apoptosis, a mechanism of physiological cell death (5) and, by this mechanism may contribute to irreversible left ventricular (LF) dysfunction.

Treatment for heart failure has improved dramatically over a short space of time. It is well recognized that the neuroendocrine response, including the renin- angiotensin and the sympathetic system, are activated in CHF (6). Interestingly, only anti-neuroendocrine treatment with angiotensine- converting enzyme (ACE) inhibition, -blockage and anti- aldosterone therapy may result in significant reduction in morbidity and mortality (7,8,9).

However, beta- blockers are pharmacologically a very heterogeneous class of agents. Carvedilol is not only unique in being the first beta- blocker for heart failure (and the only for which small doses required for initiation of treatment are available) but also has a unique pharmacological profile. Carvedilol, a multiple- action -adrenoceptor blocker, vasodilator (-blockade) and antioxidant drug, is a potent cardioprotective agent as shown in a variety of experimental models of ischemic cardiac injury (10). In experimental models, carvedilol has been shown to inhibit oxygen free radicals production and apoptosis of the myocytes (11); therefore, carvedilol in CHF might be more effective than other -blockers for its antioxidant and antiapoptotic activities which play a synergistic role with its non- specific and -blocking effects.

The aim of the present investigation was to study the influence of Carvedilol on the indices of hemorheology, hemogoagulation and lipid metabolism at patients with chronic heart failure.

Material and methods

There were 30 patients with NYHA class II or III CHF (males- 20, females- 10) after myocardial infarction aged from 42 to 67 years examined during the investigation. The investigation was performed before and after treatment. The current degree of the patient's heart failure was assessed by echocardiography (registration on Aloka- SSD- 500) by use of the following parameters: left ventricular end- diastolic volume, left ventricular ejection fraction. All patients were treated with basic therapy (glycosides+ diuretics+ ACE inhibitor) and Carvedilol was added from 3,125- 6,25 mg twice a day to 12,5- 25 mg (twice) for 12 weeks (3 months). Dosage was selected individually. The use of other drugs was excluded. Clinical characteristics of the study group are shown in Table 1. Written informed consent was obtained from all patients. Approval was obtained from the local ethics committee.

Besides, the hematocrit was measured with the help of the microcentrifuge. Deformability of red blood cells was studied with the help of viscosimeter. The thrombocytes (platelet) aggregation and disaggregation was estimated by Zakhariya and Kinakh. Serum recalcification time was measured by W. Howel, Prothrombin index- by A, Quick, fibrinogen - by R. Rutberg, fibrinolytic activity of blood - by E. Kowalski. Serum concentrations of MDA were measured by L. Andreeva. Statistical processing of obtained data was performed with the help of standard statistical (non- parameters criterion) methods. The significance changes of hemorheology, hemogoaculation and lipid metabolism parameters after administration of carvedilol was examined by the Whylcoukson- Mann- Whythny U test.

On the day of investigation, oral medication (see Table 1) was continued. Carvedilol was added from 3,125- 6,25 mg twice a day to 12,5- 25 mg (twice) for 12 weeks (3 months).

RESULTS

Before administration carvedilol the study showed the distinct and significant changes of hemorheology, hemocoagulation and lipid metabolism parameters in patients with CHF. We discovered the significant increase of fibrinigen by 20 % and hematocrit by 7,6 %; reduction of erythrocyte deformability by 14,5 %; completely depressed blood fibrinilotic activity, decrease of plasma recalcification time by 40 %; increase of protrombin index by 19 %; speeding-up of spontaneous aggregation of thrombocytes and decreased of plasma MDA by 10,7% in pts with CHF. After 12 weeks (3 months) of treatment with Carvedilol the indices were changed: the fibrinogen was decreased by 40% and the hematocrit by 16,1 %; the erythrocyte deformability increased by 24,5%; the blood fibrinolytic activity increased by 50%; the plasma recalcification time increased by 50%; the protrombin index decreased by 33%; the spontaneous aggregation of thrombocytes decreased and decreased of plasma MDA by 8,9 % in pts wit

Table 1. Patients characteristics before administration of carvedilol

Basic characteristics	
N	30
Sex (F/ M)	10/ 20
Age (year)	56,4 (42- 67)
Diagnosis	
Ischemic Heart Disease	
After myocardial infarction (n)	30
NYHA class	
II (n)	10
III (n)	20
Echocardiographic data	
Ejection fraction (%)	33,4 (25- 48)
Left ventricular end- diastolic volume (mL)	224,2 (146- 326)
Therapy (mean dosages per day)	
ACE inhibitors (n, mg)	
Enalapril	1,25 - 10 mg once per day
Diuretics (option)	
Furosemide (n, mg)	
Spironolactone (n, mg)	from 20 mg to 240 mg
Dihydochlortiazide (mg)	75- 100 mg once per day
Glycosides	25- 100 mg once per day
Digoxin (n, mg)	0,25- 0,5 mg once per day
Digitoxin (n, mg)	0,05- 0,15 mg once per day
Beta- blocker	
Carvedilol (n, mg)	from 3,125mg to 25 mg twice per day

CHF (0.05 >Pu < 0.01) (Table 2).

Discussion and conclusion

A recent study has shown that carvedilol improves the rheology properties of blood and hemocoagulation index in pts with CHF. This effect of carvedilol seems to be specific and independent from its cardio- protective effect due to -blockade; in fact, blood coagulation activity decreased after the course of treatment. The potent antioxidant

activities of carvedilol can be attributed to the presence of a carbazole
moiety in its chemical structure (12). In fact, plasma levels of MDA are significantly higher in CHF patients than in controls, both at rest and during exercise (13). Carvedilol protects against oxygen free radicals which are consistent plasma levels obtained clinically at doses between 25 to 50 mg/day. This activity results in organ protection from several oxygen free radicals mediated injuries (14-17). Thus, obtained data showed that pts with CHF has hemorheological disturbances; the main one is increase of fibrinogen level, decrease of erythrocyte deformability and increase of their aggregative properties. We can suppose that worsening of hemorheological properties of blood can predetermine the progressing of HF. In fact, the quantitative and qualitative alteration (changes) of fibrinogen is "keystone" in hemostasis and by peroxydation syndrome (18,19). Oxydativee stress is also involved in the induction of apoptosis; a mechanism of physiological cell death (5) and, by this mechanism may contribute to irreversible LV dysfunction. Thus, this mechanism arouses the "vicious circle" (18-19).

In summary, sympathetic nervous system hyperactivity provides a short -term support to the failing heart. Conversely, prolonged sympathetic activity is recognized as a fundamental process contributing to the progression of heart failure (20,21). Carvedilol is a non- selective beta-adrenergic antagonist which also blocks alpha1- receptors and has antioxidant properties (22). In patients treated with carvedilol the response to catecholamine may be significantly inhibited as this agent blocks the receptors without increasing their density (23).

The addition of Carvedilol "above" basic therapy promoted a pronounced

Index	Before treatment	After 3 months	P<
Fibrinogen (g/l)	5,18 (4 -9)	4,4 (3,2 -5,3)	0,005
Hematocrit (%)	49,3 (41- 59)	44,2 (38- 52)	0,001
Erythrocyte deformability (%)	1,44 (0,95 -1,60)	1,75 (1,6 -1,9)	0,001
Fibrinolitic activity , (min)	262,9 (214- 297)	203,1 (160 -236)	0,001
Plasma recalcification time (sec)	151,3 (94 -175)	95,6 (57-140)	0,001
Protrombin index, (%)	100,9 (94- 107)	87,4 (73- 101)	0,001
Plasma MDA (nmol/ml)	7,7	6,5	0,05
Platelet aggregation index (%)	40,1 (30,3 -60)	34,9 (32- 42)	0,001
Aggregation rate (unit/ min)	0,039 (0,018- 0,09)	0,025 (0,017- 0,09)	0,05
Platelet aggregation summary index (%)	57,1(48- 111)	42,5 (46- 83)	0,001
Platelet disaggreg ation index (%)	22,7 (18,5- 32)	16,6 (15- 23)	0,001

well, the functional disturbances of thrombocytes during the HF pathogenesis are very important and limited by offences lipid metabolism in outcome hypercatecholaminemia. The plenty of catecholamine in blood depresses the fibrinolitic activity which provocative intensified precipitation of fibrinogen and in result to show up the thrombonemia and disturbances of microcirculation (19). Simultaneously, the plenty of catetholamine is the powerful factor prognosis. The improvement of rheological properties of blood, hemocoagulation and lipid metabolism with carvedilol to eliminate the threat of thrombogenicity complication in patients with CHF.

improvement of hemorheology and hemocoagulation state, lipid metabolism

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Details about the authors.
1. National Cardiac Society of Azerbaijan,SRİ of Cardiology,after named J. Abdullayev

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