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THE EFFICACY OF DIFFERENT THERAPY PROTOCOLS FOR HEART FAILURE IN PATIENTS WITH HEART FAILURE AND INCREASED NATRIURETIC PEPTIDE LEVEL

EFIKASNOST RAZLIČITIH TERAPIJSKIH PROTOKOLA ZA SRČANU INSUFICIJENCIJU KOD PACIJENATA SA SRČANOM INSUFICIJENCIJOM I POVIŠENIM NIVOOM NATRIURETSKIH PEPTIDA

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Summary: Natriuretic peptide BNP might be clinically useful for monitoring treatment effects in patients with heart failure (HF). In order to investigate the pharmacological effects of different therapy protocols for patients with HF based on the BNP level before and after therapy, we performed an open randomized comparative trial. Sixty-two HF patients with increased natriuretic peptide level, aged 55.82±9.09, II-III NYHA functional classes, ejection fraction (EF) <45%, received a 12-week treatment with either traditional pharmacotherapy for HF with ACE inhibitors and β-blockers (1st group), or ACE inhibitors and angiotensin II receptor blockers (ARBs) (2nd group), or β-blockers and ARBs (3rd group), and ACE inhibitors, β-blockers and ARBs (4th group). We evaluated the BNP plasma level, hemodynamic state (pulmonary capillary wedge pressure (PCWP), cardiac output (CO), EF and exercise capacity. The BNP plasma level decreased significantly in the 4th group of patients who received ACE inhibitors, β-blockers and ARBs, in comparison to other groups. A beneficial influence on hemodynamic and exercise capacity was significantly pronounced in this group, compared to the other therapy regimes. In conclusion, the therapeutic protocol: ACE inhibitors, β-blockers and ARBs in HF patients with increased natriuretic peptide level significantly improves the quality of life, left ventricular function, hemodynamic parameters and exercise capacity. All these changes were accompanied with a decreasing of the BNP plasma level.

Keywords: B-type natriuretic peptide, heart failure, therapy protocols

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Kratak sadržaj: Natriuretski peptidi mogu imati klinički značaj u praćenju terapijskih efekata kod pacijenata sa srčanom insuficijencijom. Cilj ove randomizovane studije bio je da se ispita efikasnost različitih terapijskih protokola za srčanu insuficijenciju kod pacijenata sa srčanom insuficijencijom na osnovu nivoa BNP-a u plazmi pre i posle terapije. Šezdeset dva pacijenta sa srčanom insuficijencijom i povišenim nivoom BNP-a, dobi 55,82±9,09 god, sa II-III NYHA funkcionalnom klasom, ejekcionom frakcijom (EF) <45%, primali su 12 nedelja tradicionalnu farmakološku terapiju za srčanu insuficijenciju, i to: ACE inhibitore i β blokatore (1. grupa); ACE inhibitore i angiotenzin II receptor blokatore (ARBs) (2. grupa); ß blokatore i ARBs (3. grupa); ACE inhibitore, ß blokatore i ARBs (4. grupa). Ispitivali smo nivo BNP-a u plazmi, hemodinamske parametre (pritisak u plućnim kapilarima (PCWP), *cardiac output* (CO), EF i dužinu trajanja opterećenja. Nivo BNP-a u plazmi se značajno snizio u 4. grupi pacijenata, koji su bili na ACE inhibitorima, ß blokatorima i ARBs, u odnosu na ostale grupe. Takođe je primećen značajan pozitivan uticaj na hemodinamske parametre i trajanje opterećenja u toj grupi pacijenata, u poređenju sa ostalim ispitanicima. Može se zaključiti da terapijski protokol koji uključuje ACE inhibitore, ß blokatore i ARBs kod pacijenata sa srčanom insuficijencijom i povišenim BNP-om značajno poboljšava kvalitet života, funkciju leve komore, vrednosti hemodinamskih parametara i dužinu trajanja opterećenja. Sve te promene su udružene sa sniženjem nivoa BNP-a u plazmi.

Ključne reči: B-tip natriuretskog peptida, srčana insuficijencija, terapijski protokoli

Introduction

B-type natriuretic peptide (BNP) and its N-terminal propeptide (NT-proBNP) are secreted by cardiac ventricles mainly in response to myocardial stretch induced by volume load (1). The natriuretic peptide system is activated to its highest degree in ventricular dysfunction. Increased secretion of natriuretic peptides reduces blood pressure and plasma volume through a coordinated action in the brain, adrenal gland, kidney, and vasculature (2). The natriuretic peptides play an important role in HF compensation and can delay progression of the disease. Heart hypertrophy (usually appears with HF) stimulates production of ANP and BNP, and stretching of atria and ventricles stimulates release of these hormones (3–6). The mechanism of increased production of natriuretic peptides can be explained by chronic central hypervolemia with elevated ventricle filling pressure (7, 8). The natriuretic peptides protect the body from excessive quantity of salt and water, inhibit secretion and effects of vasoconstriction peptides, and influence vascular relaxation. They inhibit release of ACTH and sympaticus effect. On the peripheral level, they increase the filtration rate, diuresis, natriuresis, decrease the systemic vascular resistance and plasma volume in order to protect the heart from overload (9). In the progression of the disease vasoconstriction effects and retaining of salt and water take prevalence, and natriuretic peptides can work no longer against the sympathetic nervous system and renin-angiotensin-aldosterone system. This condition leads to appearance of the clinical signs and symptoms of heart failure. ANP and BNP plasma concentrations correlate with level of the disease, and with the New York Heart Association (NYHA) class (10). In further progression of the disease glomerular filtration and urine flow decrease, and sodium absorption increases in the proximal tubules with decreased sodium in collecting ductus where natriuretic peptides act (11). In the patients with heart failure, ANP and BNP synthesize in ventricles and atria, but their response is inadequate.

BNP has received close attention as a cardiovascular marker (12–14). It could be demonstrated that in chronic HF patients and during the subacute phases of myocardial infarction, of all tested neurohormones, the BNP and its N-terminal propeptide (NT-proBNP) were the best markers to identify heart failure and the most powerful predictors of morbidity and mortality (1). These hormones are helpful for guidance of therapy and monitoring the disease course in HF patients. Therefore, the aim of present study was to investigate the pharmacological effects of different therapy protocols for patients with HF based on the BNP level before therapy and three months after therapy.

Material and Methods

Sixty-two patients with stable chronic heart failure were selected for the study. There were 16 women and 48 men, with a mean age of 55±9.09 years. All patients were NYHA class II or III, and the cause of heart failure was ischemic in 28, and dilatative cardiomyopathic in 34, EF <45%. Before entry into the above study the patients were on a two week wash-out period for previous heart failure therapy and during that period they received diuretics, nitrates or digitalis. The exclusion criteria for the study included the presence of myocardial infarction within 60 days, potassium >5.5 mmol/L, hepatic disease (serum transaminase >3 times normal), renal impairment (creatinine >250 μmol/L). The study protocol was approved by the Ethics Committee and all patients provided written, informed consent.

All study patients were divided into four groups depending on type of therapy: group 1 (n=14) who received angiotensin-converting enzyme (ACE) inhibitors and β-blockers; group 2 (n=16) who received ACE inhibitors and angiotensin II receptor blockers (ARBs); group 3 (n=16) who received β-blockers and ARBs; and group 4 (n=16) who received ACE inhibitors, ß-blockers and ARBs. In the present study we compared the effect of different combination therapy with ACE inhibitors (enalapril 10 mg twice daily), beta-blockers (carvedilol 25 mg twice daily) and ARBs (valsartan 80 mg twice daily). The patients were followed for an additional period of three months.

Clinical measurement

A two-dimensional echocardiogram was performed on each subject, before therapy and three months after therapy, by using an Acuson Aspen ultrasound machine. EF was expressed in % and calculated by the Simpson's rule (15).

The hemodynamic variables, such as pulmonary capillary wedge pressure and cardiac output were determined by using the Swan-Ganz catheter, which was introduced transcutaneously through the internal jugular vein of each patient and advanced to a pulmonary wedge position according to pressure tracings.

The hemodynamic values were measured before, and three months after randomly allocating patients at combination therapy, at baseline in a supine position and after exercise tolerance test (bicycle ergometer exercise test in supine position in which the load was increased by 25 W at 2 min intervals).

Laboratory analysis

Blood drawn from pulmonary artery was used for measuring the BNP concentrations. For measuring BNP, the blood samples were collected in chilled EDTA tubes and then immediately centrifugated at 3000 rpm for 15 min at 4 °C, after which the plasma thus obtained was stored on dry ice and analysed within 4 hours. BNP concentrations were measured by the fluorimetric immunoassay test »Biosite« BNP-Triage®TEST (San Diego, USA) (16).

Statistics

The statistical analysis included the calculation of means ± SD, as well as the Student's t-test. The Pearson correlation coefficient was used to express association between BNP and hemodynamic variables. The multicriteria analysis, based on the parameters obtained by correlation, regressive and discriminatory analyses of the hemodynamic variables and BNP, was used to define a mathematical model for the quantitative presentation of the most favourable therapeutic protocol for the treatment of HF patients. The statistical analyses were performed with an SPSS program for Windows. P-values below 0.05 were defined as statistically significant.

Results

The results presented in *Table I* show that after treatment with ACE inhibitors and ß-blockers (group 1) the left ventricular EF was significantly increased by about 8.8% ($p<0.001$). In addition, ACE inhibitors and ß-blockers, at baseline and after exercise, significantly decreased pulmonary capillary wedge pressure (about 9.7%, $p<0.01$), and significantly increased the cardiac output (about 6.1%, $p<0.01$). Plasma BNP level was reduced (about 13.5%, $p<0.01$) during administration of ACE inhibitors and ß-blockers therapy.

As it is shown in *Table II*, after treatment with ACE inhibitors and ARBs (group 2) the left ventricular EF was significantly increased about 7.8% ($p<0.001$). At the same time, ACE inhibitors and ARBs, at baseline and after exercise, significantly decreased pulmonary capillary wedge pressure (about 13.6 %, $p<0.01$), and significantly increased the cardiac output (about 4.2 %, $p<0.01$). Plasma BNP level was reduced (about 14.9%, $p<0.01$) during administration of ACE inhibitors and ARBs therapy.

As seen from *Table III*, after treatment with ß-blockers and ARBs (group 3) the left ventricular EF was significantly increased about 7.0% ($p<0.01$). Also, ß-blockers and ARBs, at baseline and after exercise, significantly decreased pulmonary capillary wedge pressure (about 8.2 %, $p<0.01$), and significantly incre-

Table I Effects of ACE inhibitors and β-blockers on ejection fraction, BNP, hemodynamic variables and exercise capacity in heart failure patients.

Variables	Baseline	After therapy
EF (%)	29.14±3.44	31.71±2.92**
BNP (ng/mL)	418.36±212.20	361.79±171.16*
	Before exercise	
PCWP (mmHg)	15.74±1.81	13.81±1.82*
CO (L/min)	3.94±0.77	4.17±0.68*
	After exercise	
Exercise (min)	2.76±0.86	3.07±0.99*
PCWP (mmHg)	22.00±3.96	19.86±2.57*
CO (L/min)	5.16±1.25	5.47±1.10*

Data are presented as the mean value ± SD. ACE = angiotensin-converting enzyme; BNP = brain natriuretic peptide; CO = cardiac output; EF = ejection fraction; PCWP = pulmonary capillary wedge pressure * – $p<0.01$; ** – $p<0.001$ compared with baseline.

Table II Effects of ACE inhibitors and ARBs on ejection fraction, BNP, hemodynamic variables and exercise capacity in heart failure patients.

Variables	Baseline	After therapy
EF (%)	27.25±4.09	29.38±3.14**
BNP (ng/mL)	493.81±183.80	420.38±163.75*
	Before exercise	
PCWP (mmHg)	15.88±2.03	14.88±1.31*
CO (L/min)	3.60±0.54	3.37±0.52*
	After exercise	
Exercise (min)	2.48±0.82	2.66±0.80*
PCWP (mmHg)	23.88±5.69	20.63±3.79*
CO (L/min)	4.23±0.59	4.41±0.55*

ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; BNP = brain natriuretic peptide; CO = cardiac output; EF = ejection fraction; PCWP = pulmonary capillary wedge pressure * – $p<0.01$; ** – $p<0.001$ compared with baseline.

Table III Effects of β-blockers and ARBs on ejection fraction, BNP, hemodynamic variables and exercise capacity in heart failure patients.

Variables	Baseline	After therapy
EF (%)	26.75±4.70	28.63±5.14*
BNP (ng/mL)	521.75±235.41	439.06±252.40*
	Before exercise	
PCWP (mmHg)	16.25±2.05	14.13±2.16**
CO (L/min)	3.53±0.66	3.71±0.62**
	After exercise	
Exercise (min)	2.90±0.63	3.09±0.70*
PCWP (mmHg)	25.75±3.92	23.63±4.03*
CO (L/min)	4.21±0.74	4.38±0.70*

Data are presented as the mean value ± SD. ARBs = angiotensin II receptor blockers; BNP = brain natriuretic peptide; CO = cardiac output; EF = ejection fraction; PCWP = pulmonary capillary wedge pressure * – $p<0.01$; ** – $p<0.001$ compared with baseline.

Table IV Effects of ACE inhibitors, β-blockers and ARBs on ejection fraction, BNP, hemodynamic variables and exercise capacity in heart failure patients.

Variables	Baseline	After therapy
EF (%)	28.13±4.96	32.25±3.89**
BNP (ng/mL)	462.75±207.98	278.56±109.09**
	Before exercise	
PCWP (mmHg)	15.63±1.02	12.50±1.55**
CO (L/min)	3.63±0.78	4.03±0.81**
	After exercise	
Exercise (min)	3.10±0.92	3.56±0.96**
PCWP (mmHg)	24.38±4.47	20.00±4.23**
CO (L/min)	4.10±1.03	4.58±1.11**

Data are presented as the mean value ± SD ACE = angiotensin-converting enzyme; ARBs = angiotensin II receptor blockers; BNP = brain natriuretic peptide; CO = cardiac output; EF = ejection fraction; PCWP = pulmonary capillary wedge pressure * – $p<0.01$; ** – $p<0.001$ compared with baseline.

ased the cardiac output (about 4.0%, $p<0.01$). Plasma BNP level was reduced (about 15.8%, $p<0.01$) during administration of ß-blockers and ARBs therapy.

Table IV shows that after treatment with ACE inhibitors, ß-blockers and ARBs (group 4) the left ventricular EF was significantly increased about 14.6% ($p<0.001$). In addition, ACE inhibitors, ß-blockers and ARBs, at baseline and after exercise, significantly decreased pulmonary capillary wedge pressure (about 17.9 %, $p<0.001$), and significantly increased the cardiac output (about 11.7 %, $p<0.001$). Plasma BNP level was reduced (about 39.8%, $p<0.001$) during administration of ß-blockers and ARBs therapy.

To estimate the advantages of therapeutic protocols the following post-treatment parameters were selected: BNP, pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes. The parameters were analysed by using the methods of discriminatory, correlation and regression analyses. The results of discriminatory, correlation and regression analyses were used in the multicriteria analysis.

The canonical discriminatory analysis yields estimate for the validity of original classification of subjects into groups, and classification of the groups of subjects based on the values of parameters following the use of different therapeutic procedures.

Table V shows results of the discriminatory analysis applied to group classification of the subjects.

The discriminatory analysis of the subjects from group 1 (patients receiving ACE inhibitors and ß-blockers) shows that out of the total of 14 patients, 57.10% of them are correctly classified in that group based on the values of observed parameters.

Table V The results of discriminatory analysis.

Classified into:	Group into which the patient should be classified			
	Group 1	Group 2	Group 3	Group 4
Group 1	57.10	42.90	0.00	0.00
Group 2	12,50	50.00	12,50	25.00
Group 3	25.00	6,30	37.50	31.30
Group 4	12.50	25.00	12.50	50.00
48.4% real cases have been correctly classified				

The discriminatory analysis of the subjects from group 2 (patients receiving ACE inhibitors and ARBs) shows that out of the total of 16 patients, 50.00% of them are correctly classified in that group based on the values of observed parameters.

The discriminatory analysis of the subjects from group 3 (patients receiving ß-blockers and ARBs) shows that out of the total of 16 patients, 37.50% of them are correctly classified in that group based on the values of observed parameters.

The discriminatory analysis of the subjects from group 4 (patients receiving ACE inhibitors, ß-blockers, and ARBs) shows that out of the total of 16 patients, 50.00% of them are correctly classified in that group based also on the values of observed parameters.

The discriminatory analysis shows that the values of BNP, pulmonary capillary wedge pressure after exercise, minute volume after exercise, and duration of exercise in minutes, with probability of $p=0.484$, viz. $P=48.4\%$, depend on the type of therapeutic protocol used.

The values of correlation coefficients between BNP and pulmonary capillary wedge pressure after exercise, minute volume after exercise, and duration of exercise in minutes after therapy, by the groups of subjects, are shown in *Table VI*.

Analysis of the correlation coefficient of BNP value and selected parameters after therapy in group 1 shows that BNP significantly correlates with pulmonary capillary wedge pressure after exercise ($p<0.01$), cardiac output after exercise ($p<0.01$), and duration of exercise in minutes ($p<0.05$). In addition, the cardiac output significantly correlates with the duration of exercise in minutes ($p<0.01$).

Analysis of the correlation coefficient of BNP value and selected parameters after therapy in group 2 shows that BNP significantly correlates with pulmonary capillary wedge pressure after exercise ($p<0.01$), and

Table VI The values of correlation coefficients between BNP and pulmonary capillary pressure after exercise, minute volume after exercise, minute volume after exercise, and duration of exercise in minutes after therapy by groups of patients.

Group 1			
Parameter	PCWP	CO	Duration of exercise in min
BNP	0.852**	0.695**	0.645*
PCWP		0.454	0.341
CO			0.836**
Group 2			
Parameter	PCWP	CO	Duration of exercise in min
BNP	0.829**	0.389	0.586**
PCWP		0.326	0.457
CO			0.535*
Group 3			
Parameter	PCWP	CO	Duration of exercise in min
BNP	0.746**	0.426*	0.690**
PCWP		0.704**	0.892**
CO			0.556*
Group 4			
Parameter	PCWP	CO	Duration of exercise in min
BNP	0.711**	0.895**	0.793**
PCWP		0.676**	0.487
CO			0.814**

BNP = brain natriuretic peptide; CO = cardiac output; PCWP = pulmonary capillary wedge pressure; *– $p<0.01$; **– $p<0.001$

Table VII The linear regression model for BNP and pulmonary capillary wedge pressure after exercise, minute volume after exercise, and duration of exercise in minutes

	R	F	p
Group 1	0.934	22.631	0.000
Group 2	0.865	11.844	0.001
Group 3	0.878	13.421	0.000
Group 4	0.095	36.675	0.000

R = group correlation coefficient; F = Fisher's coefficient.

duration of exercise in minutes ($p<0.01$). In addition, the cardiac output significantly correlates with the duration of exercise in minutes ($p<0.05$).

Analysis of the correlation coefficient of BNP value and selected parameters after therapy in group 3 shows that BNP significantly correlates with pulmonary capillary wedge pressure after exercise ($p<0.01$), cardiac output after exercise ($p<0.01$), and duration of exercise in minutes ($p<0.05$). Moreover, the cardiac output significantly correlates with the duration of exercise in minutes ($p<0.05$). The pulmonary capillary wedge pressure significantly correlates with the cardiac output ($p<0.01$) and with the duration of exercise in minutes ($p<0.01$).

Analysis of the correlation coefficient of BNP value and selected parameters therapy in group 4 shows that BNP significantly correlates with pulmonary capillary wedge pressure after exercise ($p<0.01$), cardiac output after exercise ($p<0.01$), and duration of exercise in minutes ($p<0.01$). Furthermore, the cardiac output significantly correlates with the duration of exercise in minutes ($p<0.01$). The pulmonary capillary wedge pressure significantly correlates with the cardiac output ($p<0.01$).

The model of linear regression for BNP (dependent variable) and pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes (independent variables) after therapy, by the groups of subjects, are shown in *Table VII*.

The correlation coefficients of the selected independent parameters in group 1, with BNP value as a dependent parameter ($R=0.934$, and also the value $F=22.631$) with probability of $p=0.0001$, show that pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes have a highly significant impact on BNP value in this group of subjects.

The correlation coefficients of the selected independent parameters in group 2, with BNP value as a dependent parameter ($R=0.865$, and also the value $F=11.844$) with probability of $p=0.001$, show that pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes have a highly significant impact on BNP value in this group of subjects.

The correlation coefficients of the selected independent parameters in group 3, with BNP value as a dependent parameter ($R=0.878$, and also the value $F=13.421$) with probability of $p=0.0001$, show that pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes have a highly significant impact on BNP value in this group of subjects.

The correlation coefficients of the selected independent parameters in group 4, with BNP value as a dependent parameter ($R=0.950$, and also the value $F=36.675$) with probability of $p=0.0001$, show that pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes have a highly significant impact on BNP value in this group of subjects.

The multicriteria analysis, based on the results of correlation, regression, and discriminatory analyses of the selected parameters covered by the research, is used to define: indicators, severity of their impact (assign the weight), and mathematical model, so that the quantitatively most favourable therapeutic protocol can be established.

Indicators are: Individual significant linear correlation coefficients (ILCC); Value of the group correlation coefficient from the linear model for BNP as a dependent variable, and pulmonary capillary wedge pressure after exercise, cardiac output after exercise, and duration of exercise in minutes, as the independent variables after therapy (GLCC); Percentage of correctly classified subjects, as a result of discriminatory analysis (PCC).

Weights are: Individual significant linear correlation coefficient (ILCC), $p<0.05$; weight factor=0.75; Individual significant linear correlation coefficient (ILCC), $p<0.001$; weight factor=1; Value of the group correlation coefficient from the linear model (GLCC); weight factor=1; Value rank of Fisher's F coefficient from the linear model (RF): Rank 1, weight factor 40, Rank 2, weight factor 30, Rank 3, weight factor 2, Rank 4, weight factor 10.

Percentage of correctly classified subjects, as a result of discriminatory analysis (PCC) weight factor 1.

The mathematical model is:

$$MM=MM1+MM2$$

$$MM1=[(ILCC) * \text{weight factor}] + [GLCC * \text{weight factor}] + [RF * \text{weight factor}]$$

$$MM2=PCC * \text{weight factor}$$

The results of multicriteria analysis in the *Table VIII–XI* show the estimate of therapeutic protocol for therapeutic groups 1–4.

The mathematical model of the therapeutic protocol for group 1, is for patients receiving ACE inhibitors and ß-blockers MM1 = 127.15, MM2 = 57.10.

The mathematical model MM MM = 184.25, quantitatively presents the total therapeutic effect.

The mathematical model of the therapeutic protocol for group 2 for patients receiving ACE inhibitors and ARBs is: MM1 = 99.25<, MM2 = 50.00.

The mathematical model MM = 149.25 quantitatively presents the total therapeutic effect.

The mathematical model of therapy protocol in group 3 for patients receiving ß-blockers and ARBs is: MM1 = 113.30 and MM2 = 37.50.

The mathematical model MM = 150.80, quantitatively presents the total therapeutic effect.

Mathematical model of therapy protocol in group 4 for patients receiving ACE inhibitors, ß-blockers, and ARBs is: MM1 = 140.00, MM2 = 50.00.

The mathematical model MM = 190.00 quantitatively presents the total therapeutic effect.

Table VIII Estimate of the advantages of tharapeutic protocol.

Therapeutic group	Mathematical model	Indicator	Weight Factor	Sum Scores
Group 1	M 1 parameters			
	Significant correlation coefficient <0.05	1	0.75	0.75
	Significant correlation coefficient <0.01	3	1.00	3.00
	Value rank of Fisher's F coefficient from the linear model	2	30.00	30.00
	Value of R coefficient from the linear regression model	0.93	100.00	93.40
	M 2 parameters			
	Percentage of correctly classified subjects from the discriminatory analysis	57.10	1.00	57.10
	TOTAL			**184.25**

Table IX Estimate of the advantages of tharapeutic protocol.

Therapeutic group	Mathematical model	Indicator	Weight Factor	Sum Scores
Group 2	M 1 parameters			
	Significant correlation coefficient 0.05	1	0.75	0.75
	Significant correlation coefficient 0.01	2	1.00	200
	Value rank of Fisher's F coefficient from the linear model	4	10.00	10.00
	Value of R coefficient from the linear regression model	0.87	100.00	86.50
	M 2 parameters			
	Percentage of correctly classified subjects from the discriminatory analysis	50.00	1.00	50.00
	TOTAL			**149.25**

Table X Estimate of the advantages of tharapeutic protocol.

Therapeutic group	Mathematical model	Indicator	Weight Factor	Sum Scores
Group 3	M 1 parameters			
	Significant correlation coefficient <0.05	2	0.75	1.50
	Significant correlation coefficient <0.01	4	1.00	4.00
	Value rank of Fisher's F coefficient from the linear model	3	20.00	20.00
	Value of R coefficient from the linear regression model	0.88	100.00	87.80
	M 2 parameters			
	Percentage of correctly classified subjects from the discriminatory analysis	37.50	1.00	37.50
	TOTAL			**150.80**

Table XI Estimate of the advantages of tharapeutic protocol.

Therapeutic group	Mathematical model	Indicator	Weight Factor	Sum Scores
Group 4	M 1 parameters			
	Significant correlation coefficient <0.05		0.75	0.00
	Significant correlation coefficient <0.01	5	1.00	5.00
	Value rank of Fisher's F coefficient from the linear model	1	40.00	40.00
	Value of R coefficient from the linear regression model	0.95	100.00	95.00
	M 2 parameters			
	Percentage of correctly classified subjects from the discriminatory analysis	50.00	1.00	50.00
	TOTAL			**190.00**

Discussion

This randomized study showed that comparison of the pretreatment BNP plasma concentrations in each group of subjects with chronic stable heart failure, who were divided according to the therapeutic protocol, demonstrates that BNP concentrations in each group were higher before therapy than after therapy. The percentages of decreased mean BNP values after therapy in the groups 1, 2, 3 and 4 were 13.5%, 14.9%, 15.8% and 39.8%, respectively. In addition, in all groups HF therapy induced a reduction in the pulmonary capillary wedge pressure and increase in the cardiac output, ejection fraction and exercise capacity.

The lower plasma BNP concentrations after treatment of HF patients were also found by some other authors (18–21). The available data from studies are promising and suggest that BNP and NT-proBNP might be clinically useful for determining the optimal treatment for HF patients and for monitoring the treatment effects (22, 23). The patients with low posttreatment BNP concentrations have an excellent long-term prognosis (24). Maeda et al. (25) demonstrated that the sustained high plasma level of BNP three months after optimized treatment was an independent risk factor for mortality despite improvements in left ventricular EF and symptoms. In patients with HF, high levels of BNP have consistently been associated with poor outcome. Therefore, it is intriguing to monitor HF patients with regular assessment of BNP to identify impeding decompensation. HF medication is titrated to achieve a maximal reduction of BNP levels.

In this study, the multicriteria analysis, which was based on the parameters as obtained by correlation, regressive and discriminatory analyses of the hemodynamic variables and BNP, and aimed to define indicators, severity of their impact and mathematical model, so that the quantitatively most favourable therapeutic protocol can be established, indicated that the best total effect of therapy is reported from the therapeutic protocol of patients receiving ACE inhibitors, ß-blockers and ARBs. The therapeutic protocol of patients receiving ACE inhibitors and ß-blockers has almost the same effect as ACE inhibitors, ß-blockers, and ARBs therapeutic protocol. The therapeutic protocols of patients receiving ß-blockers and ARBs and patients receiving ACE inhibitors and ARBs have shown to be less effective than the previous two.

In conclusion, the therapeutic protocol: ACE inhibitors, b-blockers and ARBs in HF patients with increased natriuretic peptide levels significantly improves the quality of life, left ventricular function, hemodynamic parameters and exercise capacity. All these changes were accompanied with the decreasing of BNP plasma level.

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