Weight reduction decreases NT-proBNP levels in obsese coronary patients with chronic diastolic heart failure

Giuseppe Cocco[1], David Chu[2]

[1]Contracted Professor, Cardiology, University of Ferrana, Italy
[2]Cardiology Office, Rheinfelden, Switzerland

Submitted: 2 April 2007
Accepted: 8 June 2007

Arch Med Sci 2007; 3, 2: 112-116

Corresponding author:
Giuseppe Cocco, MD, FESC
POB 119, Marktgasse 10A
CH-4310 Rheinfelden 1
Switzerland
E-mail: praxis@cocco.ch

Abstract

Introduction: This study was designed to evaluate the effect of weight reduction on NT-proBNP levels in hypertensive obese patients with chronic diastolic heart failure (DHF). Obesity exerts a negative impact on the cardiovascular system and a weight reduction improves pathological changes. Circulating levels of NT-proBNP reflect left ventricular diastolic wall stress and are strongly related to mortality and treatment success in heart failure.
Material and methods: Thirty-eight hypertensive obsese patients with stable DHF were enrolled in a 6 months diet counseling program aimed to achieve a >5 kg weight reduction. Thirty-two patients with the same cardiac pathology who were unwilling to adhere to the diet were used as a control group. Blood sampling for measurement of NT-proBNP and other laboratory values, functional assessment, 6-minute walk testing, cycloergometry, and echocardiography were obtained at entry and after 6 months.
Results: In hypertensive obese patients with symptomatic DHF, a 7 kg weight and body mass index (BMI) reduction induced a fall in circulating levels of NT-proBNP, reflected by an improved diastolic dysfunction and a significant increase in the walking distance. The improvement was achieved without a negative impact on left ventricular compliance and remodeling.
Conclusions: Weight reduction improved the cardiac function in patients being treated concurrently with modern antihypertensive drugs. The effect of the cardiac improvement was comparable to that seen with pharmacological treatment programs. This supports the need to implement a weight reduction in obese hypertensive patients with chronic DHF.

Key words: natriuretic peptide, weight reduction, diastolic heart failure.

Introduction

Brain natriuretic peptide and NT-proBNP are secreted by ventricular myocytes. In the presence of the renin-angiotensin-aldosterone axis and also the sympathetic system dysfunctioning, the serum levels of brain natriuretic peptide and NT-proBNP are increased reflecting left ventricular diastolic stress. These levels are useful predictors of mortality and treatment effects in cardiac diseases [1–3]. Obesity has a negative impact on cardiac mortality, and a weight reduction improves the myocardial dysfunction of hypertensive [4] and diabetic patients with systolic heart failure [5, 6]. However, the effect of weight reduction on the cardiac function of obeses hypertensive patients with *diastolic* HF (DHF) is unknown.

The aim of this study was to assess the effect of a >5 kg weight decrease, achieved by diet counseling, on the NT-proBNP level of adipose

hypertensive patients with chronic left ventricular DHF (without left ventricular failure). Furthermore, the effects of weight reduction of NYHA functional class, 6 minute walking distance, cycloergometric data, and echocardiography were assessed.

Material and methods

Study design

The nature of the study excluded an double-blind, randomized design. However, the persons who collected and analyzed the data were blinded to group allocation.

Patients

The first criterion for selection was hypertension, diagnosed at least 12 months before selection (stable blood pressure values >150/90 mm Hg). All patients were on antihypertensive medication.

Obesity, a body mass index (BMI) >30 kg/m^2, was the second selection criterion. Patients with a BMI between 30.1 and 40 kg/m^2, corresponding to obesity grade I–II were included, those with a BMI either <30.1 or >40 kg/m^2 were excluded.

The third criterion for selection was the presence of stable DHF. The criteria for the diagnosis of this pathology are well defined, ie. a history of congestive heart failure according to the Framingham criteria with a normal systolic ventricular function (LVEF >51%), and at least a Doppler abnormality in diastolic function, including a deceleration time >250 msec [7-9].

Patients fulfilling these criteria were selected if symptoms were stable and medications (Table I) could be kept unchanged during the follow up period.

Patients with other cardiac pathologies, such as ischemic, valvular, hypokinetic or arrhythmic disease were excluded. Patients with other medical conditionssuch as peripheral vascular disease, moderate pulmonary pathology, severe renal (creatinine >2.6 mg/dl), and hepatic dysfunction (ASAT/ALAT values >300%) over the normal range were also excluded.

All patients gave their informed consent. Ethical Committee approval was obtained.

Caloric restriction

Pre-study dietary modifications related to diabetes mellitus or dyslipidemia were maintained, but calories intake was reduced to achieve a weight loss of >5 kg within 6 months. Weekly diet recommendations were given by dieticians with the supervison of a qualified physician. The adherence to this caloric restriction was a selection criterion. Patients were also encouraged to increase their physical activity, but there was no specific training program.

Thirty-eight consecutive patients accepted the caloric restriction and were selected. Thirty-two patients with the same pathology refused the diet restriction and were used as the control group.

Dietary supplementing

After 3-4 months fourteen patients (37%) had difficulties in complying with the caloric restrictions. In this case glucomannan (Konjac Mannan root) was prescribed. This dietary supplement expands to make the stomach feel full, but it is not absorbed from the intestine and does not induce any interaction with the medical treatment.

Laboratory measurements

Fasting blood samples were collected between 7:30 and 8:30 am, at baseline and after 6 months. NT-proBNP was determined using the Roche analytic system. The analytical range extended from 5 to 35000 pg/ml, with a co-efficient of variation of 1.3% at al level of 222 pg/ml and of 1.2% at a level of 4090 pg/ml. Serum creatinine, sodium values and other laboratory parameters were also collected for safety.

6-minute walk test

This test measures the exercise capacity of patients with cardiac failure [10-12] and it is an important independent factor of mortality [13]. The test is particularly practical in obese patients. The walking distance was measured at baseline and after 6 months.

Cycloergometry

Sitting cycloergometry (Marquette Hellige, CardioSys V6.01 equipment) was performed at baseline and after 6 months. A 12-lead ECG was

Table I. Concomitant medications

	Diet group n=38 (%)	No diet group n=32 (%)
ACE-inhibitor	30 (80)	26 (81)
A-II-blocker	4 (11)	3 (9)
β-blocker	26 (68)	22 (69)
thiazide like diuretic	32 (84)	29 (91)
spironolacton	5 (13)	2 (6)
amlodipin	16 (42)	13 (41)
thiazolidinediones	10 (26)	7 (22)
sulfonylurea drugs	23 (61)	20 (63)
aspirin 100 mg	15 (39)	11 (34)
allopurinol	2 (5)	1 (3)
analgesics on need	28 (88)	28 (88)

ACE – angiotensin-converting enzyme, A-II – angiotensin II

continuously monitored, and blood pressure was automatically measured every 2 min. All patients were exercised with a basal load of 20 Watts (W) with a 1-min. 10-W incremental load. Patients were encouraged to exercise until exhaustion.

Echocardiography

Measurements (Acuson Sequoia C256 equipment) were obtained at baseline and after 6 months. Resting left ventricular function was recorded to exclude the presence of systolic failure: end-diastolic (LVEDD), end-systolic (LVESD) diameters were obtained from the parasternal long axis, and LVEF was recorded. The echocardiographic evidence for diastolic left ventricular dysfunction was accepted when the mitral deceleration rate was >250 msec and the when the E/A ratio (calculated from pulsed Doppler analysis of the early filling, E, and the late filling velocity, A, of the mitral valve) was pathologic (over the age dependent range).

Statistical analysis

Statistical analyses were performed using Statgraphics Centurion XV.I package. Sample size and powers calculations were calculated prior to study begin.Data are expressed as the mean value±SD. Data were tested for normal distribution using the Kolmogorov-Smirnov test and for homogeneity of variance by using the χ^2 test. For continuous variables, intra-, and intergroup comparisons were made by the two-sided paired and unpaired Student's t-test. Intergroup differences (diet versus no diet), changes over time, and any interaction (trends over time between groups) were assesses by the ANOVA two-way repeated measures. Correlations were determined with the Spearman's or Pearson's correlation test. A p-value <0.05 is usually accepted as statistically significant, however, because of multiple comparisons we consider lower p-values as more relevant.

Results

Patients' characteristics

At selection both groups were similar for concomitant medications (Table I), age, gender, height, smoking status, concomitant pathology (Table II), weight, body mass index (BMI), NT-proBNP levels, New York Heart Association (NYHA) class, walk test distance, blood pressure, cycloergometric values, echocardiographic parameters, creatinine and sodium values (Table III).

Table II. Medical therapy

	Diet group (n=30)	Control (no diet) group (N=24)
ACE-inhibitor	21 (70%)	17 (71%)
A-II-blocker	11 (37%)	9 (38%)
β-blocker	21 (70%)	17 (71%)
diuretic	25 (83%)	20 (83%
spironolactone	20 (67%)	16 (67%)

ACE – *Standard angiotensin-converting enzyme, A-II – angiotensin II*

Weight loss and BMI

In the diet group weight decreased from 108±5.5 to 101±5.5 kg (–7 kg), a highly significant change (p<00003). Weight remained unchanged in the control group. At six months the intergroup difference was highly significant (p<0.0001).

In the diet group BMI decreased from 35±2.6 to 33±2.4 kg/m², a highly significant change (p<0.0001). BMI was unchanged in the control group. At six months the intergroup difference was higly significant (p<0.0001). Data are shown in Table III.

NT-proBNP serum levels

In the diet group, NT-proBNP decreased from 1905±405 to 1537±377 pg/ml, a highly significant change (p=0.0001). In the control group NT-proBNP did not change. At six months the intergroup difference was highly significant (p<0.00005) (Table III).

NYHA functional class

The NYHA class decreased from 2.4±0.5 to 2.1±0.4 (ns) in the diet group. In the control group the NYHA class increased slightly, but the change was not significant. At six months the intergroup difference in NYHA was highly significant difference (p<0.00005) (Table III).

6-minute walk test

In the diet group the walking distance increased from 225±20 to 251±22 meter, a highly significant change (p<0.000002). In the control group the walking distance did not change. At six months the intergroup difference was highly significant (p<0.00002) (Table III).

Heart rate and blood pressure at rest

Heart rate and blood pressure did not change to a clinically relevant extent in either group (Table III).

Cycloergometry

The work load (watt), heart rate and blood pressure did not change to a clinically relevant extent in either group. On the other hand, in the diet group diastolic blood pressure decreased from 104±3.0 to 96±1.7 mm Hg (p<0.00004). In the control group diastolic blood pressure did not

Table III. Analyzed data

	Diet Group			No Diet Group			Intergroup
	baseline	after	p-value	baseline	after	p-value	ANOVA p value
weight (kg)	108±5.5	101±5.5	<0.00003	108±4.6	108±4.5	ns	<0.00003
BMI (kg/m^2)	35±2.6	33±2.4	<0.0001	35±2.3	35±2.5	ns	<0.0001
NT-proBNP (pg/ml)	1905±405	1537±377	=0.0001	1828±341	1853±354	ns	<0.00005
NYHA class	2.4±0.5	2.1±0.4	ns	2.4±0.5	2.6±0.5	ns	<0.00005
6-minute walk test (m)	225±20	251±22	<0.000002	225±23	225±23	ns	<0.000002
HR_{rest} (beats/min)	64±4.8	64±4.3	ns	64±4.5	64±45.1	ns	ns
SBP_{rest} (mmHg)	141±2.4	137±2.0	p<005	140±2.1	140±2.5	ns	p<005
DBP_{rest} (mmHg)	88±7.0	86±4.0	ns	89±7.9	91±9.7	ns	ns
RPP_{rest}	89±8.0	88±2.5	ns	89±8.0	89±8.1	ns	ns
$Watt_{max}$	82±8.9	83±8.4	ns	82±8.3	83±7.2	ns	ns
HR_{peak} (beats/min)	116±11.1	117±10.8	ns	114±10.4	114±10.5	ns	ns
SBP_{peak} (mmHg)	185±16.9	182±13.1	ns	188±15.6	190±18.0	ns	ns
DBP_{peak} (mmHg)	104±3.0	96±1.7	<0.00004	104±9.1	104±8.2	ns	<0.00002
RPP_{peak}	215±30.1	213±27.3	ns	214±27.6	216±30.4	ns	ns
LVEDD (mm)	41±1.5	41±1.2	ns	41±1.4	42±1.3	ns	ns
LVESD (mm)	25±2.2	25±1.7	ns	25±1.8	25±1.6	ns	ns
LVEF (%)	57±2.7	57±3.1	ns	58±2.9	57±3.4	ns	ns
mitral dec time (msec)	296±13	263±18	<0.000001	293±16	295±17	ns	<0.00005
E/A ratio	0.6±0.1	0.8±0.1	ns	0.6±0.1	0.6±0.1	ns	ns
serum creatinine (µmol/l)	91±3.3	87±6.4	ns	93±4.2	94±5.0	ns	ns
serum sodium (mmol/l)	138±2.3	136±3.3	ns	137±3.5	186±4.6	ns	ns

Data are given as mean±SD; ns – not significant
BMI – body mass index, NYHA – New York Heart Association, HR – heart rate, SBP – systolic blood pressure, DBP – diastolic blood pressure, RPP – rate pressure product (SBP+HR), LVEDD – left ventricular end-diastolic dimension, LVESF – left ventricular end-systolic dimension, LVEF – left ventricular ejection fraction

change. After six months the intergroup difference in diastolic blood pressure was statistically highly significant (p<0.00002) (Table III).

Echocardiography

Systolic function: LVEDD, LVESD and LVEF did not change in either group.

Diastolic function: In the diet group the mitral deceleration time decreased from 296±13 to 263±18 msec, a highly significant change (p<0.000001). In the control group mitral deceleration time did not change. At six months the intergroup difference was highly significant (p<0.00005).

On the other hand, the E/A ratio was unchanged in either group (Table III).

Creatinine and sodium serum levels

Creatinine and sodium levels did not change in either group (Table III).

Discussion

To our knowledge this study is the first to examine the effect of a relevant weight reduction on resting levels of NT-proBNP in obese hypertensive patients with chronic diastolic HF. Our results showed that in these patients, a 7 kg weight reduction and a significant BMI reduction were effective and induced an important fall in circulating levels of NT-proBNP. This was reflected by an improved diastolic dysfunction (significant decrease in the mitral deceleration time) and a longer walking distance (6 minute walk test). At six months the NYHA functional class did not seem to change significantly. However, compared to patients without this weight reduction, the NYHA functional class seemed to be reduced. Also, the results supported the fact that the positive changes were obtained without a negative impact on left ventricular compliance and remodeling (LVEDD, LVESD, LVEF and E/A ratio were unchanged).

The weight and BMI decrease reduced the hypertensive effect of exercise on diastolic blood pressureIn contrast, there was not the antihypertensive effect on resting blood pressure described by Frolich et al. [4]. In this study, however, there was a longer period of observation (our study lasted only six months) and the antihypertensive drugs [4] differed to those used in current medical practice.

The discrepancy between the significant changes in NT-proBNP levels, walking distance, mitral relaxation time, and to some extent, NYHA functional class, and the lack of improvement in cycloergometry, systolic ventricular function, and E/A ratio might at first sight seem surprising. However, the dichotomic effect is understandable. Indeed, natriuretic peptide levels [14-16] and mitral deceleration time [7, 17, 18] are strongly related to the ventricular diastolic stress and respond rapidly to the myocardial load, while left ventricular remodeling probably needs more than six months [14-16].

Limitations of the study

The results were collected in obese patients with hypertensive DHF and they not be extrapolated to patients with other cardiac problems. Although the control group was matched for relevant characteristics, we cannot rule out selection bias, in the sense that patients unwilling to adhere to a caloric restrictions may differ from those who do. However, the major limitations of the trial were the small number of patients and the impossibility of performing a double-blind study.

Conclusions

In obese hypertensive patients with DHF the positive cardiac effect of 7 kg weight reduction was additive to the effect of modern medications. Indeed, in terms of efficacy, weight reduction improved the cardiac function to an extent comparable to complex pharmacologic treatment regimes. Thus we believe that the significant reduction in circulating concentrations of NT-proBNP and left ventricular diastolic dysfunction, coupled with an increased walking distance and some improvement in NYHA functional class, provide a good reason to implement weight reduction in these patients.

References

1. Lang CC, Choy AM, Struthers AD. Atrial and brain natriuretic peptides: a dual natriuretic peptide system potentially involved in circulatory homeostasis. Clin Sci (Lond) 1992; 83: 519-527.
2. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. Circulation 1997; 96: 509-516.
3. Latini R, Masson S, Anand I, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. Eur Heart J 2004; 25: 292-299.
4. Reisin E, Frohlich ED, Messerli FH, et al. Cardiovascular changes after weight reduction in obesity hypertension. Ann Intern Med 1983; 98: 315-319.
5. Ross R, Dagnone D, Jones PJ, et al. Reduction in obesity and related comorbid conditions after diet-induced weight loss or exercise-induced weight loss in men. A randomized, controlled trial. Ann Intern Med 2000; 133: 92-103.
6. Cocco G, Pandolfi S, Rousson V. Sufficient Weight Reduction Decreases Cardiovascular Complications in Diabetic Patients with the Metabolic Syndrome. Heart Drug 2005; 5: 68-74.
7. Vasan RS, Levy D. Defining diastolic heart failure: a call for standardized diagnostic criteria. Circulation 2000; 101: 2118-2121.
8. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part I: diagnosis, prognosis, and measurements of diastolic function. Circulation 2002; 105: 1387-1393.
9. How to diagnose diastolic heart failure. European Study Group on Diastolic Heart Failure. Eur Heart J 1998; 19: 990-1003.
10. Hamilton DM, Haennel RG. Validity and reliability of the 6-minute walk test in a cardiac rehabilitation population. J Cardiopulm Rehabil 2000; 20: 156-164.
11. Sharma R, Anker SD. The 6-minute walk test and prognosis in chronic heart failure- the available evidence. Eur Heart J 2001; 22: 445-448.
12. Enright PL. The six-minute walk test. Respir Care 2003; 48: 783-785.
13. Ingle L, Rigby AS, Carroll S, et al. Prognostic value of the 6 min walk test and self-perceived symptom severity in older patients with chronic heart failure. Eur Heart J 2007; 28: 560-568.
14. Hambrecht R, Gielen S, Linke A, et al. Effects of exercise training on left ventricular function and peripheral resistance in patients with chronic heart failure. A randomized trial. JAMA 2000; 283: 3095-3101.
15. Giannuzzi P, Temporelli PL, Corrà U, Tavazzi L; ELVD-CHF Study Group. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure: results of the exercise in left ventricular dysfunction and chronic heart failure (ELVD-CHF) trial. Circulation 2003; 108: 554-559.
16. Conraads VM, Beckers P, Vaes J, et al. Combined endurance/resistance training reduces NT-proBNP levels in patients with chronic heart failure. Eur Heart J 2004; 25: 1797-1805.
17. Tei C, Dujardin KS, Hodge DO, Kyle RA, Tajik AJ, Seward JB. Doppler index combining systolic and diastolic myocardial performance: clinical value in cardiac amyloidosis. J Am Coll Cardiol 1996; 28: 656-664.
18. Sohn DW, Chai IH, Lee DJ, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 1997; 30: 474-480.