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Research Paper

Relation between NT-proBNP and the extent of coronary artery disease in chronic heart failure patients

Medical Science

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ABSTRACT

Heart failure is accompanied by augmented plasma concentrations of BNP and NT-proBNP. In this study we investigated whether myocardial ischemia can be an additional mechanism for elevated NT-proBNP levels. Materials and methods: The study subjects consisted of 80 hospitalized patients who were allocated to a control group (N=21) or to a CHF group (N=59). All recruited subjects underwent coronary angiography (CAG) and plasma NT-proBNP levels were measured. Results: NT-proBNP levels in the CHF group were higher in patients with ischemic heart failure than in patients with CHF and no CAD (835, 46 ± 585, 45 vs. 349, 11 ± 354,08pg/ml, P=0,004 respectively). Subgroup analysis in the CHF patients showed that NT-proBNP levels tended to be positively related to number of diseased vessels, but statistical significance was only found between the no-CAD and 3 vessel disease subgroup. Conclusion: NT-proBNP levels are closely related with the presence of CAD in patients with CHF.

Introduction

Coronary artery disease is the predominant cause for heart failure. The hemodynamic expression of heart failure in patients with CAD and reduced due to ischemic events ejection fraction is elevated left ventricular end-diastolic pressure. Ventricular remodeling caused by ischemia results in reduced cardiac output and elevated cardiac filling pressures [22]. In patients with chronic heart failure with preserved ejection fraction, coronary atherosclerosis is also considered one of the main causes of diastolic dysfunction and heart failure [20].

Myocyte stretch and neurohormonal activation in patients with CHF are the main causes for the secretion of natriuretic peptides [1, 17] and originally BNP and NT-proBNP were considered biomarkers for heart failure only. More recently, there has been a growing body of data on the relevance of both biomarkers in coronary artery disease. Studies showed that transient ischemia increases wall stress and induces NT-proBNP synthesis and release in proportion to the degree of ischemic insult [17, 9]. It is widely believed that the underlying pathophysiological process for an increase in BNP and NT-proBNP values is left ventricular systolic or diastolic dysfunction caused by myocardial ischaemia leading to an increased wall stress [2, 3]. Nevertheless, data derived from experimental studies suggest a direct release of BNP and NT-proBNP from cardiomyocytes in response to myocardial ischaemia independent of ventricular wall stress. It has also been demonstrated that BNP even rises after temporary myocardial ischaemia induced by balloon inflation during coronary intervention [19]. Furthermore, three independent studies have indicated that BNP and NT-proBNP provide prognostic information on long term mortality and adverse cardiovascular events superior to that provided by traditional risk factors [5, 6, 7, 8, 10, 14, 15, 18].

Although BNP and NT-proBNP are well established biomarkers for the diagnosis and prognosis of patients with chronic heart failure, the role of natriuretic peptides as biomarkers for myocardial ischemia in these patients is still unknown.

The aim of our study was to investigate the correlation between NT-proBNP levels and the severity of coronary artery disease in chronic heart failure patients.

Materials and methods:

This study was conducted in Department of cardiology, Second MHAT – Sofia, Bulgaria and was approved by the local ethics committee. The study included patients who were referred to coronary care unit for assessment of coronary artery disease. Patients with acute coronary syndromes were excluded. Severity of CAD is defined as the number of vessels with stenosis > 50%. All patients with history of hematological, neoplastic, renal, liver, or thyroid diseases, and patients with infections and autoimmune diseases were excluded from the study, as well as patients with stroke and recent myocardial infarction (< 3 months).

A total number of 80 patients (47 men and 33 women) were recruited. Demographic data, medical treatment and history were obtained from the hospital record. Modifiable risk factors, events or complications, and current therapy were recorded. The anthropometric measurements; weight (kg), height (m), calculated body mass index (kg/m2), electrocardiogram and echocardiography were obtained. Venous blood samples were obtained from participants before CAG for determining NT-proBNP levels. The serum level of NT-proBNP was determined using the technique of Enzyme Linked Fluorescent Assay - ELFA (VIDAS NT-proBNP automated test for use on the VIDAS instrument). All recruited subjects underwent coronary angiography (CAG) and invasive measurement of left ventricular end-diastolic pressure.

Patients were allocated to a control group (N=21), comprising patients without symptoms of heart failure, with preserved ejection fraction and coronary artery stenosis of < 50% or to a CHF group (N=59), comprising patients with symptomatic heart failure, preserved or reduced ejection fraction and elevated left ventricular end-diastolic pressure.

Statistical Analysis

Clinical variables were normally distributed and expressed as mean ± standard deviation (SD). Unpaired student's t-test was used to evaluate differences in normally distributed continuous variables between the two groups. Correlation analysis between variables of the study was made by means of rho correlation coefficient r for continuous variables. The difference in variables were evaluated by the ANOVA test followed by a Bonferroni post-hoc test. P values < 0,05 were considered to be statistically significant. All calculations were made using SPSS statistical software for Windows (version 19.0).

Results

Table 1 shows the baseline characteristics of the study population. The CHF group included 59 patients aged 42 to 86 (mean 65.8 ± 10.33 years). 61 %(36) of patients in the group were men and 39% (23) were women. The control group included 21 patients, mean age was 59 ± 7 years. 52,4%(11) of them were men and 47,6% (10) were women.

Figure 1 shows the angiographic findings in both groups. Significant coronary artery disease was observed in 54,2% of the patients with CHF, defining CAD as predominant cause for heart failure, followed by arterial hypertension – 25,4% and valvular heart disease – 15,3%. In the CHF group most of the patients were without significant CAD or with 1-vessel disease (45, 8% and 27, 1% respectively), whereas the patients with 2 and 3- vessel disease were 11, 9% and 15, 3%.

Serum NT-proBNP levels were significantly higher in the CHF group compared to the control group (192, 04 ± 95, 17 vs. 612 ± 243, 02 pg/ml, P=0,001). NT-proBNP levels in the CHF group were higher in patients with ischemic heart failure than in patients with CHF without CAD (835, 46 ± 585, 45 vs. 349, 11 ± 354,08pg/ml, P=0,004 respectively). Subgroup analysis in the CHF patients showed that NT-proBNP levels tended to be positively related to number of diseased vessels (P=0, 03), but statistical significance was only found between the no-CAD and 3 - vessel disease subgroup (P=0, 001) (Figure 2).

Significant positive correlation between serum NT-proBNP and the number of diseased coronary arteries was observed in the CHF group and the best fit line equation estimated that for each coronary vessel, an increment of NT-proBNP of 219 pg/ml (100 - 337 pg/ml) was observed. The highest NT-proBNP levels were measured in patients with multivessel disease and chronic heart failure.

Table 2 shows the results of linear-regression analysis of other risk factors for coronary artery disease. None of them, except NT-proBNP is related to the extent of CAD in patients with chronic heart failure.

Significant positive correlation between NT-proBNP levels and LVEDP was observed in both groups (P=0,003). For each 56,30 pg/ml increment of serum NT-proBNP, left ventricular end-diastolic pressure increased with 1 mmHg (Figure 3).

Discussion

It has been proposed that BNP and NT-proBNP could identify either heart failure or left ventricular systolic dysfunction. In fact, natriuretic peptides are really indicators of raised intracardiac filling pressures, irrespective of the etiology: left ventricular systolic dysfunction, myocardial hypertrophy or myocardial ischemia. The results in this study add a new application for estimation of NT-proBNP as a marker for assessment of the severity of coronary artery disease in chronic heart failure patients. Elevated NT-proBNP levels indicate elevated left ventricular filling pressures, which in patients with ischemic CHF are due to a larger myocardial ischemic area. This explains the correlation between the levels of natriuretic peptides and the extent of CAD in chronic heart failure patients, demonstrated in the study and may partly explain the association between elevated NT-proBNP and adverse outcomes.

Weber et al. [21] referred to use the plasma level of BNP for predicting the severity of coronary artery disease. Similar finding are described by Palazuolli et al. in patients with non-ST-elevation myocardial infarction [13]. For Sadanandan et al. among patients with UA/NSTEMI, elevated BNP levels are associated with tighter culprit stenosis and LAD involvement. These findings suggest that elevated BNP may be associated with a greater severity and extent of myocardial ischemic territory [16]. Hamyshayev et al. also described strong correlation between NT-proBNP levels and the severity of coronary artery disease in patients with acute coronary syndromes [4]. Our results are consistent with these findings, although we investigated patients with stable coronary artery disease and chronic heart failure. A Japanese study suggests that NT-proBNP can be used as a biomarker with negative predictive value for CAD [11]. Nishikimi et al. revealed that N-terminal proANP, but not ANP or BNP, was independently associated with coronary artery stenosis However, the sensitivity, specificity, and positive and negative predictive values of each peptide were not sufficiently high to be used for prediction [12].

The results reported in our study are in agreement with the studies mentioned above. The serum NT-proBNP levels in chronic heart failure patients are directly related to the left ventricular filling pressures and the severity of coronary artery disease in these patients. However, the relation between these level changes and CAD severity in patients with chronic heart failure requires further evaluation.

Table 1. *Characteristics of the study population. Risk profile of participants in both groups*

	CHF (n= 59)	Control group (n=21)
Arterial hypertension	88.1% (52)	71.4% (15)
Diabetes mellitus	22% (13)	28.6% (6)
Smokers	35.6 % (21)	57.1% (12)
Dyslipidemia	35.6% (21)	52.4% (11)
BMI > 25 kg/m^2)	47.5% (28)	52.4% (11)
Family history of CAD	39% (23)	42.9% (9)

Table 2. *Relation of risk factors with the extent of CAD*

Factor	Standartized Beta	P value
NT - proBNP	,440	,000
Gender- male	-,100	,043
Age	-,053	,346
Diabetes mellitus	,193	,071
Arterial hypertension	-,120	,183
Dyslipidemia	-,023	,431
Family history of CAD	-,020	,440
Smoking	-,244	,031
Peripheral vascular disease	-,199	,065
Cerebrovascular disease	,065	,311

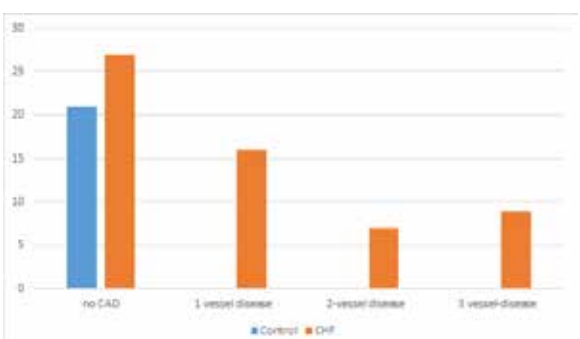

Figure 1. *Distributions according to significant angiographic findings in both groups*

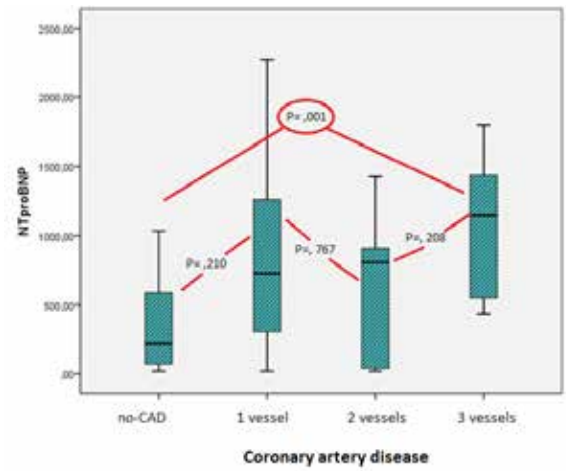

Figure 2. *NT-proBNP levels in Chronic heart failure group*

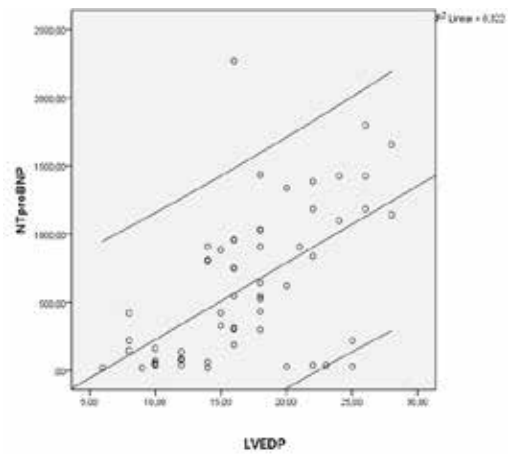

Figure 3. *Correlation between serum NT-proBNP levels (pg/ml) and LVEDP of patients subjected to coronary angiogram in both groups*

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