HVM BIOFLUX

Human & Veterinary Medicine
International Journal of the Bioflux Society

Natriuretic peptide and diastolic heart failure in the elderly

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Abstract. Objective: To determine the possible correlation of amino-terminal pro B natriuretic peptide (NT-proBNP) and other factors with the diastolic dysfunction (DD) in elderly diagnosed with heart failure (HF). Material and methods: 87 Patients aged over 65 years, diagnosed with HF, were included in study. Biochemical markers and imagistic parameters were determined, and the presence or absence of comorbidities was noted. Results:. The logistic regression has determined the odd ratio (OR) and the confidence interval 95% (CI 95%) for studied factors: Log NT-proBNP – OR 2.6, CI 95% 1.3-5, p=0.004; anemia – OR 1.1, CI 95% 0.5-2.5, p=0.75; low estimated glomerular filtration rate (eGFR) – OR 3, CI 95% 1.1-8, p=0.02; age – OR 0.8, CI 95% 0.77-1.02, p=0.1; arterial hypertension – OR 1.2, CI 95% 0.5-3.3, p=0.59; atrial fibrillation - OR 1.2, CI 95% 0.61-2.65, p=0.51; coronary disease - OR 1.7, CI 95% 0.71-4.06, p=0.22: diabetes - OR 0.7, CI 95% 0.24-2.4, p=0.64; sex OR 1.8, CI 95% 0.84-3.93, p=0.12. Conclusion: NT-proBNP and eGFR were associated with severe DD in elderly with HF.

Key Words: elderly, diastolic dysfunction, amino-terminal atrial natriuretic peptide.

Rezumat. Obiectiv: determinarea unei posibile corelaţii dintre peptidul natriuretic amino-terminal tip pro B (NT-proBNP) şi alţi factori cu disfuncţia diastolica (DD) la vârstnicii cu insuficienţă cardiacă (IC). Material şi metode: Pacienţii cu vârsta peste 65 ani, diagnosticaţi cu IC, au fost incluşi în studiu. Markeri biochimici, parametrii imagistici au fost determinaţi şi s-a notat prezenţa sau absenţa unor comorbidităţi. Rezultate: 87 de pacienţi au fost incluşi. Regresia logistică a determinat odd ratio (OR) şi intervale de confidenţă 95% (CI 95%) pentru parametrii studiaţi: Log NT-proBNP – OR 2.6, CI 95% 1.3-5, p=0.004; anemia – OR 1.1, CI 95% 0.5-2.5, p=0.75; rata filtrării glomerulare estimată joasă (eRFG) – OR 3, CI 95% 1.1-8, p=0.02; vârsta – OR 0.8, CI 95% 0.77-1.02, p=0.1; hipertensiunea arterială – OR 1.2, CI 95% 0.5-3.3, p=0.59; fibrilaţia atrială - OR 1.2, CI 95% 0.61-2.65, p=0.51; boala coronariană - OR 1.7, CI 95% 0.71-4.06, p=0.22: diabetul zaharat - OR 0.7, CI 95% 0.24-2.4, p=0.64; sexul OR 1.8, CI 95% 0.84-3.93, p=0.12. Concluzii : NT-proBNP şi eRFG joasă au fost asociate cu DD severă la vârstnicii cu IC.

Cuvinte cheie: vârstnici, disfuncţie diastolică, peptid natriuretic atrial amino-terminal.

Introduction. Heart failure (HF) is a complex physiopathological condition, in which the heart is not capable anymore to ensure an adequate cardiac flow, necessary for the metabolic needs of the human body, or, it can realize that only by increasing the filling pressure.

The prevention and treatment of HF is a complex problem with national and global implications. The American Heart Association (AHA) showed that every year more than 550000 new cases of HF appear. AHA states that more than 33 billions dollars were spent in 2007 for the treatment of HF (Rosamond et al 2007). The European Society of Cardiology (ESC) estimates that, in 2008, there were 15 millions cases of HF in a European population of 900 millions. If we add the diastolic dysfunction (DD), the number increases to 35 millions cases (Dickstein et al 2008).

HF is a major health problem in the elderly. Between 6 and 10% of people aged over 65 years have HF. The Framingham Study showed an increased prevalence with the age, from 1% in people aged 50 years, to 10% in elders over 80 years. ESC data also showed that HF is present in 10-20 % of the people aged over 80 (Dickstein et al 2008). HF is the most often encountered cause of hospitalization in the elderly. Approximately

80% of hospitalizations for HF are people aged over 65 (Yamasaki et al 2003). The DD is responsible for about 40-50% of the HF patients, over 60 old (Wong et al 1989).

The diagnostic of diastolic HF is based on the presence of symptoms and signs of HF, the normal ejection fraction (EF) and the objective evidence of left ventricle DD (Redfield 2007). Although tissue Doppler imaging is a newer technique that can determine more accurately the presence and severity of DD, the Doppler echocardiography is the method of choice for the diagnostic of DD (Redfield et al 2003). There are several clinical conditions associated with DD (arterial hypertension, coronary disease, diabetes, atrial fibrillation). Elevated levels of amino-terminal brain natriuretic peptide (NT proBNP) have been found in patients with DD (Dahlström 2004; Hunt et al 2009; Shah et al 2009).

Aim. Our study evaluated the correlation of several factors with the severity of DD in elderly, in an attempt to improve the diagnostic accuracy.

Material and Methods. The study included consecutive patients hospitalized in the 5th Medical Clinic, Municipal Clinic Hospital of Cluj-Napoca, from May 2008 to May 2009, diagnosed with HF.

The diagnostic of HF was validated by the presence of two or more major Framingham criteria (paroxysmal nocturnal dyspnea or orthopnea, jugular venous distention, rales or acute pulmonary edema, cardiomegaly, hepatojugular reflex) or two or more minor criteria (nocturnal cough, ankle edema, exertional dyspnea, pleural effusion, hepatomegaly, tachycardia (>120 bpm) (Redfield 2007).

Echocardiography was performed in order to establish the ejection fraction of left ventricle, the presence and severity of DD and valvular heart diseases. The assessment of DD was made using the E/A ratio (E=early filling, A=atrial filling). An E/A ratio less than 0.75 was quantified as mild dysfunction or impaired relaxation, while an E/A ratio more than 1.5 was defined as severe dysfunction or restrictive disorder (Redfield et al 2003). Patients with ejection fraction lower than 40% were excluded, together with subjects with moderate or severe valvulopathies.

Age, sex, estimated glomerular filtration rate (eGFR – calculated with modification of diet in renal diseases (MDRD) formula (Levey et al 2003)), the presence of anemia, coronary disease, atrial fibrillation, arterial hypertension and diabetes were selected as variables in the multivariate statistical analysis in order to predict the severity of DD. Anemia was defined, in conformity with World Health Organization, as the hemoglobin value less than 12 mg/dl in women, and less than 13 mg/dl in men. A eGFR value less than 60 ml/min/1.73 m^2 was considered pathological. NT-proBNP (pg/dl) was determined by immunochemical method with detection by electrochemiluminescence (ECLIA).

The statistical analysis was performed with the use of SPSS software version 14. For the base comparison of the primary variable we used the T test for independent variables (continuous variables) or Chi square test (dichotomic variables). We used logistic regressions for the univariate and multivariate analysis of relation between studied factors and DD. The power of determination for each factor was established by Wald parameter. The results of the logistic regression were reported as odds ratios (OR and 95% confidence intervals (95% CI). To establish a cutoff value for NT-proBNP, in relation with the severity of DD, a Receiver Operating Characteristic (ROC) curve was calculated. The value of the p parameters less than 0.05 was considered statistically significant.

Results. A total of 87 patients were selected for the study (mean age + standard deviation 77.3 ± 6.2 years; median age 77; range 65-91). A number of 57 (65.5%) patients were females and 29 (33.3%) males. History of anemia, coronary disease, atrial fibrillation, diabetes, and arterial hypertension were present in 45%, 78%, 47%, 17%, and 72% of the subjects, respectively. A pathological eGFR was found in 54% of patients.

The characteristic of the subjects in mild DD and severe DD groups are shown in Table 1. Only low eGFR and NT-proBNP were statistically significant correlated with the severity of DD (p=0.002, respectively p<0.001).

Table 1

Characteristics of patients with mild DD vs. those with severe DD

Characteristic	*Mild DD N(%) n=69*	*Severe DD N(%) n=18*	*P*
Male	21 (24)	8 (9)	0.4
Female	48 (55)	10 (11)	0.4
Age	77.4	77.1	0.88
Anemia	28 (32)	11 (12)	0.19
Coronary disease	54 (62)	16 (18)	0.95
Atrial fibrillation	31 (35)	10 (11)	0.59
Diabetes	13 (14)	2 (2)	0.67
Arterial hypertension	49 (56)	14 (16)	0.78
Low eGFR	31 (35)	16 (18)	0.002
NT-proBNP (Mean)	2313	3538	<0.001

We created binary logistic regressions for the univariate analysis of the relation between age, sex, anemia, coronary disease, atrial fibrillation, diabetes, arterial hypertension, low eGFR, NT-proBNP and the DD. The values of NT-proBNP suffered a logarithmic transformation, because of the asymmetry of the distribution (skewness – 3.34, standard deviation 0.25). Univariate logistic regressions calculated several parameters for age (OR=0.99, CI 95%=0.91-1, p=0.88), for sex (OR=1.35, CI 95%=0.79-2.29, p=0.25), for anemia (OR=1.51, CI 95%=0.82-2.58, p=0.12), for coronary disease (OR=0.98, CI 95%=0.52-1.84, p=0.96), for atrial fibrillation (OR=1.23, CI 95%=0.73-2.08, p=0.42), for diabetes (OR=0.73, CI 95%=0.33-1.64, p=0.44), for arterial hypertension (OR=1.19, CI 95%=0.64-2.2, p=0.56), for low eGFR (OR=3.13, CI 95%=1.47-6.77, p=0.004), for Log NT-proBNP (OR=2.51, CI 95%=1.5-4.19, p<0.001).

A multivariate binary logistic regression was composed in order to analyze the correlation of all searched factors with DD. Log NT-proBNP and low eGFR were the only factors statistically significant linked to the severe DD (OR=2.6, p=0.004, respectively OR=3.03, p=0.025). The Wald coefficient was higher for log NT-proBNP compared with low eGFR. The Cox & Snell R^2 coefficient was 0.302, and the Nagelkerke R^2 coefficient was 0.472. The model proposed explains 30.2% of the dependent variable.

Table 2

Multivariate predictors of DD

	Wald	*P*	*OR*	*CI 95% Lower*	*Upper*
Log NT-proBNP	8.080	0.004	2.602	1.346	5.032
Anemia	0.101	0.750	1.143	0.503	2.596
Low eGFR	5.015	0.025	3.033	1.149	8.008
Age	2.628	0.105	0.890	.773	1.025
Arterial hypertension	0.289	0.591	1.297	0.502	3.348
Atrial fibrillation	0.426	0.514	1.276	0.614	2.650
Coronary disease	1.448	0.229	1.704	0.715	4.062
Diabetes	0.211	0.646	0.765	0.244	2.403
Sex	2.366	0.124	1.826	0.848	3.934

A ROC curve was calculated in order to determine the cutoff value of NT-proBNP (Figure 1). The cutoff value was 635 pg/dl, with a sensitivity of 94.4% and a specificity of 65.2%. The area under curve (AUC) coefficient was 0.8, p<0.001, CI 95%=0.7-0.9.

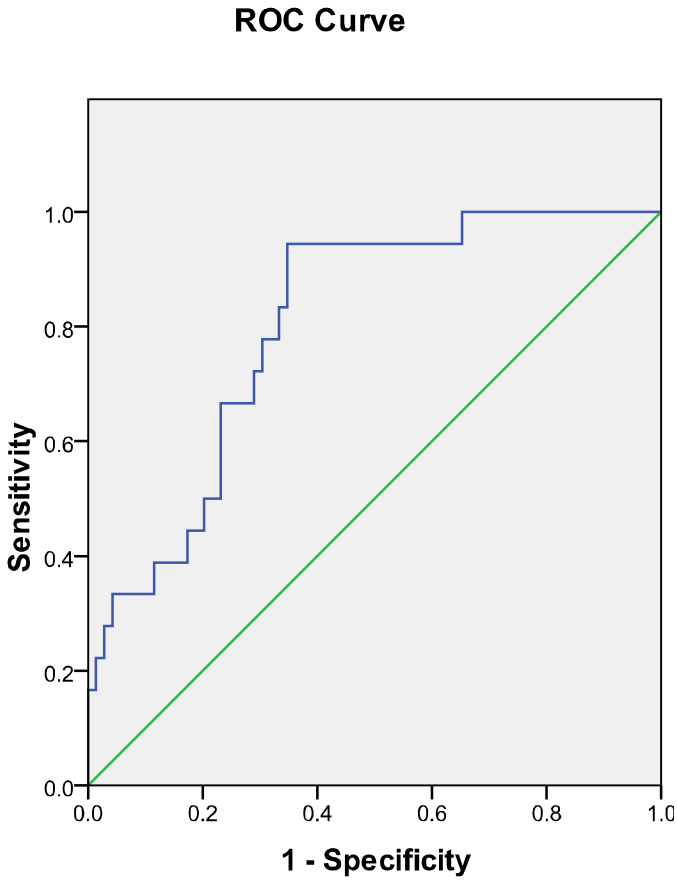

Figure 1. ROC curve for NT-proBNP

Discussion. Our study determined that NT-proBNP and low eGFR are predictors for the presence and severity of HF with normal ejection fraction. Low GRF had a higher OR, but the Wald coefficient determined that NT-proBNP had a greater contribution to the proposed predictive model. We found no association between the severity of DD and age, sex, presence of anemia, atrial fibrillation, coronary disease, arterial hypertension, and diabetes.

In our study we determined that NT-proBNP was the strongest predictor of DD in an elderly population. Roongsritong et al draw a similar conclusion, with the difference that they found a positive correlation between the gender and the high value of natriuretic peptide (Roongsritong et al 2005). Other study showed no difference association between NT-proBNP and the gender (Maisel et al 2003). We found a cutoff value for NT-proBNP of 635 pg/dl, which can predict with 94% sensitivity the severe DD. Grewal et al used a cutoff value of 600 pg/dl for the correlation with severe DD (Grewal et al 2008).

NT-proBNP is an inactive form of the brain natriuretic peptide. The main stimulus for the synthesis of NT-proBNP is an exaggerated elongation of myocardial fibers (Weber et al 2006). Besides HF, there are several diseases that can produce an elevated level of NT-proBNP by stressing the ventricular wall: acute coronary syndrome, atrial fibrillation, pulmonary embolism, chronic renal disease. In the elderly, the additional myocardial fibrosis, that inevitably occurs, and the diastolic dysfunction are known factors that contribute to the high value of NT-proBNP (Redfield et al 2002; Galasko et al 2005). NT-proBNP cannot differentiate between systolic or diastolic dysfunction. However, a low level of NT-proBNP, correlated with a normal systolic function (determined by ultrasonography) in a patient with signs and symptoms of HF, can rule out a severe DD.

Elevated level of natriuretic peptides in elderly with a normal EF, with established Framigham criteria for HF, are correlated with DD describe by echocardiography (Lubien et al 2002).

Our study revealed that low eGFR is strongly associated with the severity of DD. Miyazato et al showed the fact that the progress of DD is higher in patients with chronic renal disease and this progression is enhanced by the presence of diabetic nephropathy (Miyazato et al 2005). Other studies conclude that patients with low eGFR have a higher prevalence of both diastolic and systolic dysfunction, and DD is bound to appear in the early stage of HF (Agarwal et al 2003).

A low GFR is frequently associated with HF. The association is even greater in the elderly. The causes for a low GFR is usually intricated: renal hypoperfusion, treatment with diuretics, ACE inhibitors, other diseases (e.g. diabetes). In the early stages of HF, GFR is maintained by an elevated filtration rate. In the late stages of HF, GFR becomes dependent of the afferent arteriolar flux, neurohormones, and of the stimulation of hemodynamics (Hillege et al 2000). The mechanisms that might explain the negative influence of the low GFR on HF, include peripheral and myocardial hypoxia, elevated levels of proinflammatory cytokines, resistance to erythropoietin, acceleration of left ventricle hypertrophy and dilatation, aberrant ventricular remodelation, salt retention (Luthi et al 2006).

For years, the general belief was that HF is a disease strictly associated with a depreciated EF. In the last decade, DD has been recognized as responsible for as much as 50% of the hospitalization for HF (Hunt et al 2009). In the elderly, DD is present in a much larger proportion than in adults. The high prevalence of HF in the elderly may be associated with the changes that take place in the myocardium, that affect directly the diastolic function. Aging is associated with decrease of the elastic layer of the heart and great vessels, which can determine an increase in systolic blood pressure and myocardial stiffness. The relaxation and compliance of heart muscles decline with advanced age. Other diseases, frequently met in the elderly (atrial fibrillation, diabetes, coronary disease), may contribute to the incidence of HF (Dickstein et al 2008). Therefore is necessary to establish models which can predict the severity of DD in the elderly, in order to achieve a quick evaluation and an adequate treatment.

The limitations of our study include: technical limitations did not allow us to evaluate the E/A ratio from 0.75 to 1.5 (normal or moderate dysfunction), the left atrial volume; the evaluation of DD could not include tissue Doppler imaging; the number of patients included was relatively small; we could not established the diagnostic of obesity; the estimation of GFR was made using the values of blood creatinine, that perhaps did not estimate accurately the real GFR.

Conclusions. The assessment of NT-proBNP and cardiac ultrasonography might provide a better stratification regarding the progression of HF and could be a valuable tool for an aggressive treatment. Additional estimation of GFR can improve the accuracy of DD diagnostic.

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Received: 20 May 2009. Accepted: 10 July 2009. Published: 17 July 2009.
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How to cite this article:
Macarie A., Vesa Ș. C., 2009 Natriuretic peptide and diastolic heart failure in the elderly. HVM Bioflux 1(1):37-43. Online version available at: http://www.hvm.bioflux.com.ro/docs/2009.1.37-43.pdf