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NT-proBNP level in the diagnosis of isolated left ventricular diastolic dysfunction in patients with documented coronary artery disease

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Abstract

Background: *The diagnostic value of NT-proBNP for left ventricular (LV) systolic dysfunction is well established. However, its role for diastolic dysfunction (DD) diagnosis in patients with preserved systolic function has not been clearly defined.*

Methods: *A total of 83 patients with documented coronary arterial disease following anterior myocardial infarction and with a left ventricular ejection fraction (LVEF) > 45% were enrolled. According to echocardiographic mitral inflow and right upper pulmonary vein flow, DD was excluded in 32 patients (group A). The patients with DD were divided into three subgroups: B_1 — 38 patients with impaired relaxation, B_2 — 8 patients with pseudonormalisation and B_3 — 7 patients with restrictive inflow. In all patients E-wave propagation (Vp) and NT-proBNP were determined.*

Results: *Mean LVEF was 56.2 ± 9% and did not differ between the subgroups. NT-proBNP levels were 107 ± 101 pg/ml in group A, 299 ± 281 pg/ml in B_1, 734 ± 586 pg/ml in B_2 ($p < 0.05$ vs. A) and 2322 ± 886 pg/ml in B_3 ($p < 0.01$ vs. A and $p < 0.01$ vs. B_2). Propagation Vp was 69 ± 21 cm/s, 56 ± 20 cm/s, 53 ± 17 cm/s ($p < 0.05$ vs. A) and 44 ± 11 cm/s ($p < 0.01$ vs. A) respectively. A positive correlation was found for DD degree with NT-proBNP level ($r = 0.66$; $p < 0.001$) and negative with Vp ($r = –0.41$; $p < 0.001$). ROC curves were constructed to determine the NT-proBNP level cut-off point for DD (> 131 pg/ml, area under the curve: 0.63) and advanced restrictive DD (> 1670 pg/ml, area under the curve: 0.83) diagnosis. Sensitivity, specificity, accuracy and positive and negative predictive values were 71%, 50%, 63%, 69%, 52% and 57%, 99%, 95%, 80%, 96% respectively.*

Conclusions: *In patients with coronary artery disease and preserved LV systolic function a single NT-proBNP measurement helps to identify those with isolated DD, especially those with advanced restriction.* (Folia Cardiol. 2006; 13: 620–625)

Key words: diastolic dysfunction, echocardiography, NT-proBNP

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Introduction

Diastolic left ventricular (LV) dysfunction is present in over 35% of patients with heart failure symptoms [1, 2]. Diastolic heart failure (DHF) is especially common in the elderly and individuals with concomitant hypertension, diabetes or aortic stenosis. It is more frequent in females. Isolated DHF diagnosis is, according to the ESC Task Force, based on heart failure symptoms in the presence of normal or mildly decreased left ventricular ejection fraction (LVEF ≥ 45–50%) and evidence of abnormal relaxation or LV diastolic stiffness [3]. Currently there are no easily implemented and precise criteria for relaxation disturbance or wall stiffness assessment. The method of choice in DHF diagnosis is echocardiography with mitral inflow indices, right upper pulmonary vein flow and mitral annulus movement using spectral, colour-coded or tissue Doppler. The limitations of these techniques arise from coexisting atrial fibrillation, frequent ventricular and supraventricular ectopy or other clinical parameters such as age, LV filling pressure, heart rate and underlying heart disease [4].

The increase in the number of patients with coronary artery disease and diastolic dysfunction (DD) has made it imperative that research be conducted for new simple methods of diagnosis [5, 6].

Impaired LV filling pressure, the main factor contributing to DD, causes heart neurohormone release. The key role is held by brain natriuretic peptide (BNP) synthesised in the ventricular myocardium. Recently published data has revealed the high diagnostic value of BNP and its biologically active part N-terminal proBNP (NT-proBNP) in systolic heart failure [7–9]. The role of these peptides in DD diagnosis has recently been investigated [10, 11] and significant correlations with the degree of DD have been found in patients with low LVEF [12]. Understanding of NT-proBNP behaviour in isolated left ventricular DD is, however, limited.

The aim of the study was to assess the usefulness of NT-proBNP in the diagnosis of isolated LV diastolic dysfunction in patients with documented coronary disease and preserved LV systolic function with different patterns of mitral flow abnormality in Doppler echocardiography. Secondly, we tried to compare two DD indices, namely NT-proBNP and E-wave propagation, for identification of a pseudonormal mitral inflow pattern

Methods

Eighty-three consecutive patients (54 males of mean age 56.4 ± 10 years), who had had a documented anterior wall myocardial infarction at least 6 months earlier, had been treated with early percutaneous coronary intervention and had a current LVEF > 45%, were enrolled [4]. Significant coronary lesions were defined as left main stenosis > 50% and > 70% in the other coronaries.

Echocardiography was performed in typical apical views with a VIVID 7 (GE Vingmed, Norway) machine. Systolic and diastolic LV volumes were calculated according to the Simpson method. LVEF was calculated as a percentage of the difference in systolic and diastolic volume.

A spectral pulse-wave Doppler probe was placed in four-chamber apical view at the apex of the mitral valve cusps for mitral inflow assessment including maximal velocity of early inflow (E wave), maximal velocity of atrial flow (A wave) and deceleration time of early flow (DT). Next, the probe was placed in the right upper pulmonary vein (RUPV) at a point 1–2 cm from its opening to the left atrium for flow assessment (Fig. 1). This parameter was used to differentiate normal and pseudonormal mitral inflow [1] on the basis of the assumption that higher diastolic left atrial pressure correlates with maximal RUPV flow velocity during systole (S), diastole (D) and atrial contraction (Ar).

The widely recognised index of LV diastolic dysfunction, that of E-wave propagation (Vp), was assessed in a four-chamber view with colour-coded M-mode. After optimalisation of the area of interest at Nyquist limit the velocity of the inflow wave was registered at the segment from mitral annulus to 4 cm in the apical direction. The propagation was calculated as the slope of a line parallel to the red and blue border in M-mode.

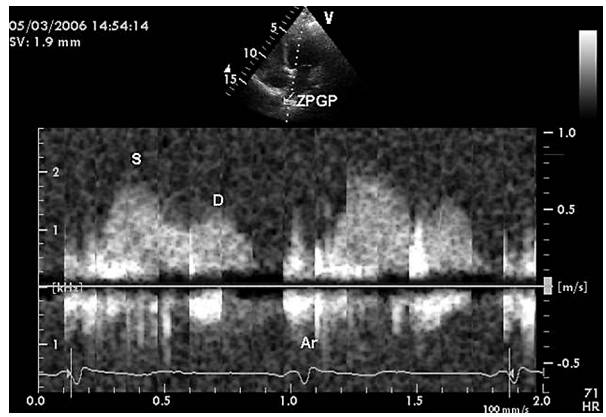

Figure 1. Normal pulmonic vein flow in right upper pulmonary vein (pulse wave Doppler); S-wave — systolic forward flow, D-wave — diastolic forward flow, Ar — atrial reversed flow, ZPGP — right upper pulmonary vein

On the basis of mitral and RUPV indices, as put forward by Madinov et al. [5] and Appleton et al. [13], patients were divided into four subgroups. Group A had normal diastolic function, while the other three groups had DD, group B_1 impaired relaxation, group B_2 pseudonormalisation and group B_3 restrictive inflow. Abnormal relaxation was recognised when the E/A ratio was < 1.0 and DT > 220 ms, pseudonormal patterns when the E/A ratio was 1–2, DT 150––220 ms, S/D < 1 and Ar > 35 cm/s. and restriction when the E/A ratio was < 1 and DT < 150 ms.

In all patients, shortly after echocardiographic examination, blood was drawn for NT-proBNP assessment with chemiluminescent immunoassay kit (Roche Diagnostics) on an Elecsys 2010 analyser.

Statistics analysis

Data are presented as means and standard deviations, or absolute numbers and percentages where appropriate. Distribution was checked with the Kolmogorow-Smirnow, Lilliefors and Shapiro--Wilks-W tests. Comparisons between means were performed with Student's t-test or Mann-Whitney-U and Kolmogorow-Smirnow tests. For qualitative data χ^2 with Yates' correction was used. Linear regression and Spearman's correlation coefficient were determined. Parameters which differed significantly between one group and the next were used to construct a logistic regression model with quasi-Newton estimation.

Sensitivity, specificity, predictive values and accuracy were determined for NT-proBNP dichotomising values from the ROC curves to diagnose any DD and advanced DD.

Results

The characteristics of the 83 enrolled patients are presented in Table 1. A significant negative correlation was found for E-wave propagation velocity and NT-proBNP ($r = -0.44$ $p < 0.00005$). A significant positive correlation was between the patient's age and NT-proBNP ($r = 0.66$, $p < 0.000009$).

According to mitral inflow and right upper pulmonary vein flow, two groups were distinguished: group A — 32 patients with normal flow and group B — 51 patients with impaired flow. Depending on the degree of LV DD, group B was divided into three subgroups: B_1 — 36 patients with relaxation mitral flow, B_2 — 8 patients with a pseudonormalisation pattern and group B_3 — 7 patients with a restrictive profile.

These subgroups did not differ in age or LVEF, although groups A and B_1 tended to have a higher ejection fraction. Mean Vp in group A was higher than in group B ($p < 0.02$) (Table 2) and decreased in consecutive subgroups $B_{1–3}$ in keeping with DD severity. Significant differences were found for Vp in group A in comparison with subgroup B_2 ($p < 0.006$) and B3 ($p < 0.003$).

Mean NT-proBNP was significantly higher in group B ($p < 0.05$) (Table 2). NT-proBNP increased with increasing DD severity: in group B_1 — 299 ± ± 281 pg/ml ($p < 0.05$ *vs.* A), in group B_2 — 734 ± ± 586 pg/ml ($p < 0.01$ *vs.* A) and in group B_3 — 2322 ± ± 886 pg/ml ($p < 0.006$ *vs.* B_2, $p < 0.002$ *vs.* A).

Table 1. Characteristics of patients.

Number	83
Age (years)	59.6 ± 10
Male	69.9%
Body mass index	26.6 ± 3.9
Diabetes	14.5%
Nicotinism	46.9%
Hypercholesterolaemia	51.8%
Hypertension	44.6%
Multivessel disease	27.3%
Propagation velocity [cm/s]	60 ± 21
E-wave [cm/s]	76.1 ± 18.5
A-wave [cm/s]	74.1 ± 24.0
E/A	1.19 ± 0.69
E-wave deceleration time [ms]	244.9 ± 84.8
Left ventricular end-diastolic volume [ml]	104.5 ± 33.7
Left ventricular end-systolic volume [ml]	47.8 ± 22.4
Left ventricular ejection fraction	56.1 ± 8.1%
NT-proBNP [ng/ml]	461.1 ± 918.9

E-wave — early mitral inflow peak velocity, A-wave — atrial mitral inflow peak velocity, E/A — ratio of early to atrial mitral inflow peak velocity

Table 2. Value of NT-proBNP propagation in patients with isolated diastolic dysfunction.

	Group A	Group B	Group B_1	Group B_2	Group B_3
Propagation [cm/s]	69 ± 20	54 ± 19	56 ± 20	54 ± 17	44 ± 11
NT-proBNP [pg/ml]	107 ± 101	645 ± 135	299 ± 281	734 ± 586	2322 ± 886

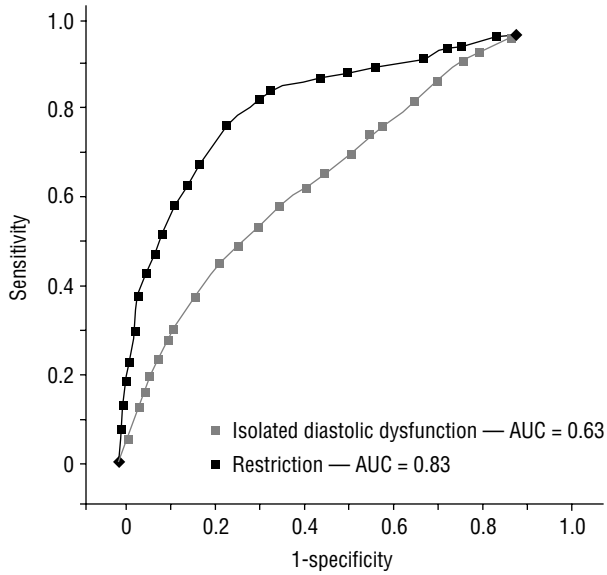

Figure 2. ROC curves of NT-proBNP for distinguishing early diastolic dysfunction and advanced diastolic dysfunction — restriction; AUC — area under the curve

For the whole population studied a significant positive correlation was found between NT-proBNP and degree of DD ($r = 0.66$, $p < 0.006$).

According to ROC analysis the best discriminating factor for DD diagnosis was NT-proBNP value > 131 pg/ml and the best value for the restrictive form of DD was NT-proBNP > 1670 pg/ml. The areas under the ROC curve for these two discriminating values were 0.63 and 0.83 respectively (Fig. 2). Sensitivity, specificity, accuracy and positive and negative predictive values were 71%, 50%, 63%, 69%, 52% and 57%, 99%, 95%, 80%, 96% respectively.

Separate analysis was performed of patients with normal mitral inflow in whom a pseudonormal profile could be diagnosed on the basis of NT-proBNP > 332 pg/ml with 85% accuracy, 62.5% sensitivity and 97% specificity. Accordingly, an E-wave propagation velocity of E < 53 cm/s distinguished patients with mild dysfunction with 66% accuracy, 78% sensitivity and 59% specificity. The area under the ROC curve for NT-proBNP was larger than for E-wave velocity (0.83 *vs.* 0.63).

The logistic regression analysis incorporated parameters significantly related to DD: demographic and coronary disease risk factors and NT-proBNP revealed that only NT-proBNP and body mass index were independent predictors of DD with an odds ratio of 1.28 (CI 95% 1.16–1.42) for every unit NT-proB-NP level increase.

Discussion

Doppler echocardiography is the most frequently used method for diastolic function assessment with mitral inflow parameters with a high correlation with haemodynamic studies [14, 15]. However it has limited value in differentiating normal inflow from the pseudonormal, representing the sum of left atrial pressure increase and relaxation disturbances [16]. Additional RUPV flow analysis helps to differentiate these two profiles [17, 18]. Unfortunately high quality measurements and precise interpretation require of the examiner long experience and deep knowledge, especially of the factors influencing the parameters under assessment, including LV afterload, heart rate, respiratory phase, LV filling pressure, ejection fraction, pharmacotherapy and patient age [4, 19, 20].

Natriuretic peptides are released into the blood in response to increased wall tension, mainly of the left ventricle. Some recent publications have therefore suggested that higher levels of natriuretic peptides, especially NT-proBNP, could become a marker of isolated DD [21, 22]. However, the populations studied are small and have consisted of patients with various DD aetiologies. The results of our study confirm the high value of single NT-proBNP assessment in patients with coronary artery disease for isolated DD diagnosis. Tschope et al. [1] have, in a recent paper, revealed a similar sensitivity of 69% for DD recognition. Despite the very similar cut-off value for NT-proBNP (120 pg/ml), we obtained significantly lower values for DD exclusion. The differences are probably due to characteristics of the population studied, that in the Tschope study having only 34% of patients with confirmed coronary disease. The level of natriuretic peptides was found to be increased in patients with coronary artery disease [23]. Our study population was also older with presumed higher levels of NT-proBNP.

The very high NT-proBNP levels in patients with a restrictive mitral inflow pattern were significantly different from those in the other subgroups. The mean value of 2322 pg/ml in these patients is similar to that described by Tschope et al. [1], who for left ventricular DD used both echocardiographic and direct pressure measurements. The high specificity and very high (96%) negative predictive value helps to exclude advanced isolated LV DD with NT-proBNP assessment. This has been confirmed by others [24]. NT-proBNP measurement is also useful in differentiating normal mitral flow from

a pseudonormal pattern, a scenario which is difficult in baseline Doppler echocardiography indices analysis. NT-proBNP level is better then early mitral flow propagation, which, despite a high negative correlation with invasive measurements in experimental and clinical studies, is dependent on the patient's age, heart rate and LVEF. The E-wave propagation velocity cut-off point (53 cm/s) is higher then that recommended by other studies (45 cm/s), probably because of the relatively high LVEF [18].

Logistic regression analysis revealed that only NT-proBNP and body mass index were independent predictors for DD diagnosis, with an odds ratio of 1.28 for every unit of NT-proBNP growth. The influence of obesity on heart failure progression is well known [25], although obese patients have lower levels of natriuretic peptides because of higher BNP clearance, with higher fat cell endopetidase activation leading to faster BNP degradation, or decreased myocardial synthesis [26, 27].

Limitations

The number of patients in more advanced LV DD is relatively small. The study lacks invasive pressure and volume measurements, the gold standard for DD assessment.

Conclusions

In patients with coronary heart disease and preserved LV systolic function a single NT-proBNP measurement helps to identify patients with isolated DD, especially those in the most advanced restrictive phase. NT-proBNP better differentiates patients with pseudonormal mitral flow profile than does the proposed E-wave propagation assessment.

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