

Urinary NT-proBNP Level: Relationship With Ventricular Function Parameters in Heart Failure

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Introduction and objectives. The plasma N-terminal probrain natriuretic peptide (NT-proBNP) level is a sensitive marker of ventricular dysfunction. The diagnostic and prognostic value of urinary NT-proBNP measurement has been demonstrated. The objective of this study was to determine the relationship between established parameters of ventricular function and the urinary NT-proBNP level.

Methods. The study involved 74 patients with heart failure (54 male, age 66 [12] years). A Doppler echocardiographic study was performed to measure atrioventricular plane displacement (AVPD), ejection fraction, mitral flow propagation velocity, and E/A. Urinary and plasma NT-proBNP levels, and the plasma aldosterone level were measured.

Results. In the whole group, the plasma NT-proBNP level was 948 (961) pg/mL, the urinary NT-proBNP level was 88.7 (17.8) pg/mL, and the aldosterone level, 165 (145) pg/mL. There were correlations between urinary NT-proBNP level and AVPD ($r=-0.5$; $P<.0001$), ejection fraction ($r=-0.3$; $P<.01$), and mitral flow propagation velocity ($r=-0.24$; $P<.05$). On dividing AVPD and ejection fraction measurements into quartiles, respectively, the urinary NT-proBNP levels for these quartiles were Q1: 103 (28) pg/mL, Q2: 89 (9) pg/mL, Q3: 86 (9) pg/mL, and Q4: 78 (9) pg/mL ($P<.0001$) and Q1: 101 (26) pg/mL, Q2: 85 (12) pg/mL, Q3: 83 (10) pg/mL, and Q4: 85 (11) pg/mL ($P<.05$), respectively. Multiple linear regression analysis showed that the plasma NT-proBNP level was an independent predictor of the urinary NT-proBNP level ($P<.0001$). When the plasma NT-proBNP level was excluded, AVPD and ejection fraction appeared as alternative independent predictors ($P<.05$).

Conclusions. There is a correlation between the urinary NT-proBNP level and left ventricular function

parameters. This study supports the use of the urinary NT-proBNP level as a biochemical marker of ventricular function in heart failure patients.

Key words: Heart failure. Natriuretic peptides. Echocardiography.

NT-proBNP en orina y su relación con los parámetros de la función ventricular en la insuficiencia cardiaca

Introducción y objetivos. La concentración plasmática de N-terminal propéptido natriurético cerebral (NT-proBNP) es un marcador sensible de disfunción ventricular. Se ha demostrado el valor diagnóstico y pronóstico de sus concentraciones urinarias. Nuestro objetivo es determinar la relación entre parámetros consolidados de la función ventricular y concentraciones urinarias de NT-proBNP.

Métodos. Hemos estudiado 74 pacientes diagnosticados de insuficiencia cardiaca (54 varones, edad 66 ± 12 años). Se les realizó un estudio eco-Doppler y se determinaron el desplazamiento del plano auriculoventricular (DPAV) (mm), la fracción de eyección (FE), la velocidad de propagación del flujo mitral (Vp) (cm/s) y la relación E/A. Se midieron las concentraciones plasmáticas y urinarias de NT-proBNP y las de aldosterona (pg/ml).

Resultados. Para toda la población, los valores plasmáticos de NT-proBNP fueron 948 ± 961 pg/ml, los urinarios 88,7 ± 17,8 pg/ml y los de aldosterona 165 ± 145 pg/ml. Correlacionamos las concentraciones urinarias de NT-proBNP con el DPAV ($r = -0,5$; $p < 0,0001$), la FE ($r = -0,3$; $p < 0,01$) y con Vp ($r = -0,24$; $p < 0,05$). Dividimos los valores de DPAV y FE en cuartiles y en cada uno calculamos el NT-proBNP urinario (C1: 103 ± 28, C2: 89 ± 9, C3: 86 ± 9, C4: 78 ± 9; $p < 0,0001$ y C1: 101 ± 26, C2: 85 ± 12, C3: 83 ± 10, C4: 85 ± 11; $p < 0,05$). Al realizar un análisis de regresión lineal múltiple se muestra que NT-proBNP plasmático es un factor pronóstico independiente de NT-proBNP urinario ($p < 0,0001$). Si excluimos

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el NT-proBNP plasmático surgen de manera alternativa, como factores pronóstico independientes, el DPAV y la FE ($p < 0,05$).

Conclusiones. El NT-proBNP en la orina se correlaciona con parámetros de función del ventrículo izquierdo. Este estudio da soporte al papel del NT-proBNP urinario como marcador bioquímico de la función ventricular en pacientes con insuficiencia cardiaca.

Palabras clave: *Insuficiencia cardiaca. Péptidos natriuréticos. Ecocardiografía.*

ABBREVIATIONS

AVPD: atrioventricular plane displacement
EF: ejection fraction
NT-proBNP: N-terminal probrain natriuretic peptide
Vp: mitral flow propagation velocity

INTRODUCTION

Heart failure is one of the most important public health problems of Western countries because of its incidence, prevalence, and high mortality rate.¹ The importance of the neurohormonal mechanisms involved in the pathophysiology of heart failure is now recognized, and this has led to advances in treatment.²⁻⁴

The natriuretic peptides have invited much interest since they are of diagnostic and prognostic importance.⁵⁻⁷ Currently, three types of natriuretic peptide are known to be present in the circulatory system: atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and type-C natriuretic peptide (CNP). These hormones are found in several tissues, but are mainly synthesized and stored in cardiomyocytes. Brain natriuretic peptide—that of greatest clinical importance—was first isolated in pig brains in 1988⁸ before being found in the human brain and in greater quantities in the ventricles of the heart.⁹ Brain natriuretic peptide is secreted mainly in response to increases in pressure and/or blood volume in the left ventricle. It is synthesized as a prohormone that is later cleaved by a protease to give rise to an amino-terminal fragment (amino-terminal probrain natriuretic peptide or NT-proBNP), and a mature peptide corresponding to the biologically active molecule BNP. The plasma concentrations of BNP and NT-proBNP are sensitive markers of ventricular hypertrophy and left ventricular dysfunction.¹⁰

Recently, studies have appeared on the diagnostic value of the urinary concentration of NT-proBNP in patients with left ventricular systolic dysfunction,¹¹ and as a prognostic factor in heart failure.¹² However, none of these papers has determined the relationship between the urinary NT-proBNP concentration and the values of

ventricular functional variables. The hypothesis of the present work was that the urinary NT-proBNP concentration is related to ventricular systolic and diastolic functional variables in patients with heart failure. Urinary NT-proBNP concentrations were therefore recorded in patients with this condition and compared with atrioventricular plane displacement (AVPD) values, the ejection fraction (EF), the mitral flow propagation velocity (Vp), the E/A ratio, and the concentration of aldosterone.

METHODS

Patients

The study subjects were 74 consecutive patients diagnosed with heart failure¹³ (54 men, age 66 (12 years) recruited from the hospital setting; most of these patients were already known. Forty seven percent had been diagnosed with ischemic heart disease, 36% with dilated heart disease, 15% with hypertensive cardiopathy, and 2% with valve disease. Each patient was subjected to a physical examination, an electrocardiogram (ECG), Doppler echocardiography, and a chest x-ray. Blood and urine samples were taken for biochemical analysis.

All patients were functionally classified according to the criteria of the New York Heart Association¹⁴ (14% fell into functional class I, 67% into functional class II, and 19% into functional class III) and all received stable medical treatment for at least one month before inclusion in the study (in accordance with the criteria of the European Society of Cardiology),¹³ some 77% with diuretics, 73% with beta-blockers, 69% with angiotensin converting enzyme inhibitors (ACE inhibitors), 43% with anti-aldosterone agents, 23% with digoxin, 17% with angiotensin II receptor antagonists (ARA-II), and 16% with calcium antagonists.

Subjects with atrial fibrillation, acute coronary syndrome, chronic or acute liver disease, chronic infections, kidney disease, and chronic obstructive pulmonary disease were excluded.

The study was performed in agreement with good clinical practice guidelines and with the standards established for human experimentation by the Declaration of Helsinki. All patients gave their written, informed consent to be included in the study.

Echocardiographic Study

Images were obtained using a standard echocardiograph apparatus with 2.5-4 MHz transducers. All echocardiographic results and Doppler traces were recorded on videotape for later analysis using a computerized system (Eco-Dat; Software de Medicina SA) without knowing the results of the other tests performed.

The A and E waves of the mitral velocity spectrum were measured by pulsed Doppler analysis at the leaflet tips; the E/A ratio was then calculated. The Vp was measured using the method of García et al.¹⁵ The EF was determined using the area-length method¹⁶ and calculated using the formula:

$$100 \times (\text{end diastolic volume} - \text{end systolic volume}) / \text{end diastolic volume}.$$

The AVPD was determined in M mode, using a two-dimensional apical projection (two and four chamber views).¹⁷ This was measured in the septal, lateral, posterior, anterior regions and the mean AVPD calculated for each.

Determination of NT-proBNP in Urine, NT-proBNP in Serum, and Aldosterone

Blood samples were taken by venipuncture with the patients lying supine for 30 min. The urine samples taken were all of first morning urine. All samples were immediately centrifuged at 1300 rpm at 4°C for 10 min, divided into aliquots, and stored at -80°C for later analysis. Before analysis, the urine aliquots were centrifuged three times at 13 200 rpm at 4°C for 30 min to avoid possible interference from the precipitation of salts in the determination of the NT-proBNP concentration.

Plasma and urine NT-proBNP concentrations were determined in duplicate by electrochemiluminescent immunoanalysis (Elecsys 2010 from Roche Diagnostics, Germany) based on the sandwich technique.¹⁸ The results (the means of two assays) were expressed in pg/mL.

Plasma aldosterone concentration was measured by radioimmunoanalysis and the results expressed in pg/mL.

Statistical Analysis

Quantitative variables were expressed as the mean (standard deviation [SD]). The normality of the distribution of the variables was analyzed using the Kolmogorov-Smirnov test. Spearman correlation coefficients were calculated to determine the relationships between the urinary NT-proBNP concentration and the studied ventricular function variables and aldosterone concentration. The Kruskal-Wallis analysis of variance test was used to compare the urinary NT-proBNP concentrations corresponding to the quartiles of the ventricular function variables studied.

Multivariate linear regression was used to test the independent power of prediction of the serum NT-proBNP, the ventricular function variables, and other variables on the urinary NT-proBNP concentration. All these variables were introduced using the Enter method; this consists of introducing all independent variables into the model at once. Variables reported to influence

the concentration of the peptide, such as sex, age, serum NT-proBNP concentration, cardiovascular risk factors (obesity, hypertension, diabetes), creatinine level, AVPD, EF and Vp were used as independent variables; the urinary NT-proBNP concentration was used as the dependent variable.

A *P* value less than .05 was considered significant. SPSS software 11.5 was used for all calculations (SPSS Inc., Chicago, Illinois).

RESULTS

The mean serum NT-proBNP concentration was 948 (961) pg/mL, the mean urinary NT-proBNP concentration 88.7 (17.8) pg/mL, and the mean aldosterone concentration 165 (145) pg/mL. Table 1 shows the patients' general and clinical characteristics.

The urinary NT-proBNP concentration was found to be negatively correlated with the AVPD ($r=-0.5$; $P<.0001$) (Figure 1), EF ($r=-0.3$; $P<.01$) (Figure 2) and Vp ($r=-0.24$; $P<.05$) (Figure 3). However, no relationship was found between the urinary NT-proBNP concentration and the E/A ratio ($P=.2$). In addition, no relationship was found between the aldosterone concentration and the urinary NT-proBNP concentration ($P=.9$), nor between the former and the ventricular function variables, although its relationship with EF was close to significance ($r=-0.2$; $P<.07$).

When the AVPD values were divided into quartiles and the corresponding urinary NT-proBNP concentrations compared (C1: 103 [28] pg/mL, C2: 89 [9] pg/mL, C3: 86 [9] pg/mL, C4: 78 [9] pg/mL), significant differences

TABLE 1. Clinical Characteristics of the Patients*

Variables	Patients (n=74)
Sex, male	54 (73%)
Age, years	66 (12)†
Systolic blood pressure, mm Hg	125 (20)†
Heart rate, beats/min	75 (12)†
NYHA	
I	14%
II	67%
III	19%
Echocardiographic variables	
EF	37 (10)†
E/A	1 (0.6)†
Vp, cm/s	27 (9)†
Serum NT-proBNP, pg/mL	948 (961)†
Urinary NT-proBNP, pg/mL	88.7 (17.8)†
Aldosterone, pg/mL	165 (145)†

*AVPD indicates atrioventricular plane displacement; E/A, E wave/A wave; EF, ejection fraction; NYHA, New York Heart Association; Vp, mitral flow propagation velocity.

†Data expressed as means (standard deviation).

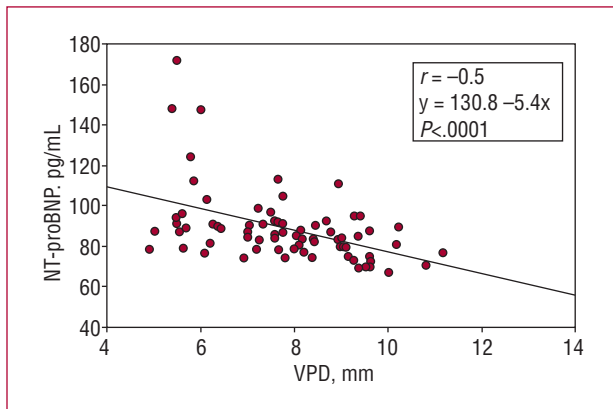


Figure 1. Inverse correlation between urinary NT-proBNP concentration and AVPD. AVPD, atrioventricular plane displacement; NT-proBNP, N-terminal pro-brain natriuretic peptide.

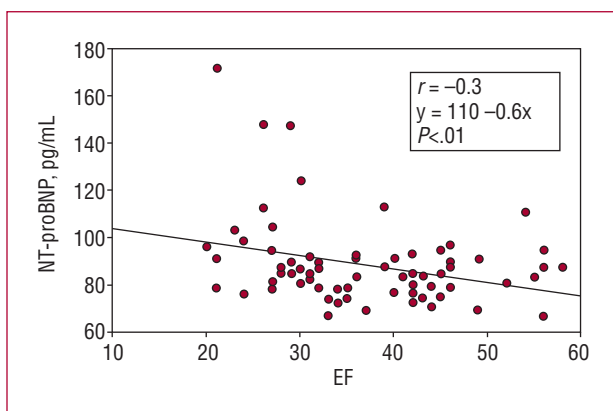


Figure 2. Inverse correlation between urinary NT-proBNP concentration and EF. EF indicates, ejection fraction; NT-proBNP, N-Terminal pro-brain natriuretic peptide.

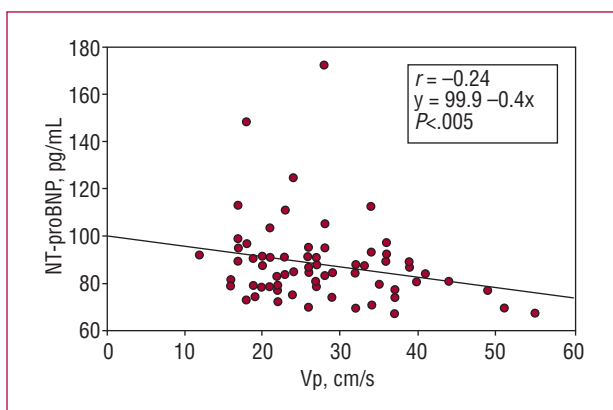


Figure 3. Inverse correlation between urinary NT-proBNP concentration and Vp. NT-proBNP, N-terminal pro-brain natriuretic peptide; Vp, mitral flow propagation velocity.

were recorded ($P < .0001$) (Figure 4). When the EF was divided into quartiles (C1: 101 [26] pg/mL, C2: 85 [12] pg/mL, C3: 83 [10] pg/mL, C4: 85 [11] pg/mL) further

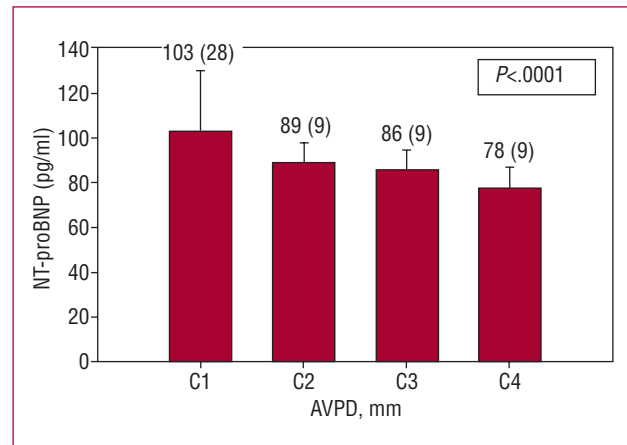


Figure 4. Comparison of urinary NT-proBNP concentrations corresponding to AVPD quartiles. AVPD, atrioventricular plane displacement; NT-proBNP, N-terminal pro-brain natriuretic peptide.

significant differences were seen ($P < .05$). No significant differences were seen when the Vp results were treated in the same way.

In the multiple linear regression analysis, the best model was obtained with the serum NT-proBNP (independent variable) and urinary NT-proBNP (dependent variable) concentrations (adjusted $r^2 = 0.694$; $P < .0001$); thus, the serum NT-proBNP concentration explains the greater part of the urinary NT-proBNP concentration.

A close relationship was seen between AVPD and EF ($r = 0.8$; $P < .0001$); colinearity was seen between these two ventricular function variables (both of which were included in the multivariate regression analysis as independent variables). When a new linear regression analysis was performed, including all the factors mentioned above except for the serum NT-proBNP concentration, AVPD and EF (when introduced separately) (Tables 2 and 3) appeared as prognostic factors independent of the urinary NT-proBNP concentration (adjusted $r^2 = 0.192$, $P < .05$, and adjusted $r^2 = 0.176$, $P < .05$ respectively).

DISCUSSION

The natriuretic peptides are powerful markers of hypertrophy^{19,20} and/or ventricular dysfunction.^{21,22} These peptides are characterized by their natriuretic, vasodilatory and anti-mitogenic properties and are secreted in response to wall stress and ventricular pressure.²³ Although cardiomyocytes are the main source of BNP, the cells of the kidney tubule also produce this peptide. Thus, urinary concentrations might reflect both myocardially-produced and renally-synthesized BNP.²⁴ Myocardially-synthesized BNP can be cleared in two ways: enzymatic degradation

TABLE 2. Results of Linear Regression Analysis*

	Non-Standardized Coefficients		Standardized Coefficients	<i>t</i>	<i>P</i>
	Beta	EE	Beta		
(Constant)	98.184	22.385		4.386	.000
Sex	0.057	5.470	0.001	0.010	.992
Age	0.442	0.246	0.276	1.794	.080
Obesity	-4.501	7.010	-0.095	-0.642	.524
Hypertension	0.459	5.965	0.013	0.077	.939
Diabetes	3.995	5.186	0.110	0.770	.445
Creatinine	0.383	3.700	0.015	0.103	.918
Vp	0.138	0.381	0.058	0.363	.719
AVPD	-5.531	2.163	-0.471	-2.557	.014

*AVPD indicates atrioventricular plane displacement; EE, standard error; Vp, mitral flow propagation velocity.

TABLE 3. Results of Linear Regression Analysis*

	Non-Standardized Coefficients		Standardized Coefficients	<i>t</i>	<i>P</i>
	Beta	EE	Beta		
(Constant)	78.710	20.366		3.865	.000
Sex	4.701	5.349	0.121	0.879	.384
Age	0.516	0.254	0.323	2.028	.051
Obesity	-6.926	6.920	-0.146	-1.001	.323
Hypertension	-2.459	5.544	-0.068	-0.444	.660
Diabetes	4.196	5.239	0.115	0.801	.428
Creatinine	-0.106	3.752	-0.004	-0.028	.978
Vp	-0.067	0.355	-0.028	-0.190	.850
EF	-0.729	0.308	-0.382	-2.369	.022

*EE indicates standard error; EF, ejection fraction; Vp, mitral flow propagation velocity.

via the action of neutral endopeptidases, and endocytosis followed by lysosomal degradation.²⁵ Renal clearance is less important for the C-terminal fragment of the peptide than the N-terminal fragment (NT-proBNP).²⁶ This all suggests that the plasma and urinary concentrations of these peptides may not be related. However, in earlier studies we showed a good correlation between plasma and urine NT-proBNP concentrations.¹²

A number of studies have shown the importance of plasma NT-proBNP in the diagnosis of heart failure and ventricular dysfunction.¹⁰ Recently, its importance with respect to ventricular function, mortality and valve regurgitation has been reported within the framework of the PRIDE study.⁷ However, there have been very few studies on the presence of these peptides in the urine and its clinical significance.^{27,28} It has been shown, however, that NT-proBNP is detectable in the urine of patients with heart failure and even in control subjects.^{11,12}

The present work set out to relate the urinary NT-proBNP concentration with different ventricular function

variables. One of these variables was AVPD, which reflects the longitudinal function of the left ventricle and is a consolidated and valuable marker of ventricular systolic and diastolic function.²⁹⁻³¹ Its use is even more valuable in patients in whom left ventricular function must be quantified but who have a poor acoustic window and in whom the identification of the endocardial boundaries is difficult. Another variable chosen was the Vp; this is relatively independent of the preload reflecting ventricular relaxation, shows a linear behavior (unlike other diastolic function variables),¹⁵ and its value diminishes with deteriorating ventricular function.³² This facilitates its comparison with biochemical variables showing similar behavior. The EF and the E/A ratio are ventricular function reference variables.

The present results show that as AVPD, EF and Vp diminish, the urinary NT-proBNP concentration increases. This supports the idea that urinary NT-proBNP is a biochemical marker of ventricular dysfunction. In addition, when the AVPD and EF values were divided into quartiles, significant differences were found in the corresponding NT-proBNP concentrations.

No relationship was found between the aldosterone concentration and either the urinary NT-proBNP concentration or the ventricular function variables—although the relationship between aldosterone and the EF was close to being significant. In this regard it should be remembered that many of the present patients were receiving anti-aldosterone treatment, ACE inhibitors, or ARA II drugs.

To determine which variables affected the urinary NT-proBNP concentration, multiple linear regression was performed. This showed the serum NT-proBNP concentration to be an independent predictor of the urinary concentration, largely explaining the latter's values (adjusted $r^2=0.694$; $P<.0001$). When the serum concentrations of the peptide were removed from the analysis, the AVPD and EF appeared (separately) as independent prognostic factors of the urinary NT-proBNP concentration (explaining 19% [$P=.014$] and 18% [$P=.022$] of this concentration respectively).

A limitation of this study is seen in that the Roche Elecsys 2010 apparatus used was originally designed to measure serum NT-proBNP concentrations. However, the good results obtained in this and in earlier work¹² suggest this machine can be used with urine samples. In addition, the patients all received conventional treatment, and some drugs can reduce NT-proBNP concentrations. However, this study confirms there to be a certain degree of neurohormonal activation in patients with heart failure undergoing apparently adequate medical treatment. It should also be noted that the significant differences between the urinary NT-pro-BNP concentrations for the AVPD ($P<.0001$) and EF ($P<.05$) quartiles implicitly involves some degree of overlap, although the quartiles with the highest mean values were associated with the lowest NT-proBNP concentrations. It should also be

remembered that the measurement of ventricular function would have been more precise had magnetic resonance or three dimensional echocardiography been used.^{32,33} However, the validity of Doppler echocardiography measurements has been extensively demonstrated,³⁴ and in the present study all were made by a specialist cardiologist.

CONCLUSIONS

The results show that the urinary NT-proBNP concentration is related to the values of different ventricular function variables; this work therefore provides evidence supporting the use of the urinary-proBNP concentration as a marker of ventricular function in heart failure. This could provide a relatively simple, non-invasive method for investigating ventricular function, especially in patients in whom collecting plasma samples is difficult.

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