

Value of NTproBNP Concentration in an Out-Of-Hospital Adult Population

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Introduction. The diagnosis of chronic heart failure (CHF) is based on demonstrating the cardiac origin of clinical manifestations. Echocardiography is the method of choice for the detection of left ventricular systolic dysfunction (LVSD). Brain natriuretic peptide (BNP) rises during LVSD.

Objectives. To analyze the plasma concentration of N-terminal brain natriuretic propeptide (NTproBNP) in a general adult population in relation to different spontaneous circumstances and to study its capacity for identifying patients with LVSD.

Methods. A cardiological examination was made and plasma NTproBNP levels were measured in a randomized group of 203 people (49-81 years old) from the Community of Valencia.

Results. The average NTproBNP concentration was 52.2 ± 98.2 pmol/l. NTproBNP levels varied with age, gender and functional stage (NYHA). The highest NTproBNP values were observed in people who had previously suffered from acute pulmonary edema or who had an ejection fraction (EF) of less than 40%. There was also a significant elevation in patients with nocturnal dyspnea, orthopnea, atrial fibrillation, $EF \leq 50\%$, angina, and ankle edema. The best concentration of NTproBNP for differentiating $EF \leq 50\%$ was 37.7 pmol/l, with 92% sensitivity and 68% specificity.

Conclusions. The elevation of NTproBNP concentration indicates the cardiac origin of clinical manifestations and serves to select patients for echocardiographic examination. Low NTproBNP concentrations help to rule out LVSD.

Key words: Chronic heart failure. Natriuretic peptides.

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Valor del nivel de NTproBNP en población adulta extrahospitalaria

Introducción. El diagnóstico de insuficiencia cardíaca crónica se basa en la demostración del origen cardíaco de las manifestaciones clínicas. El ecocardiograma es el método de elección para la detección de disfunción sistólica ventricular izquierda (DSVI). El péptido natriurético cerebral se incrementa durante la DSVI.

Objetivo. Estudiar las concentraciones plasmáticas del N terminal propéptido natriurético cerebral (NTproBNP) en un grupo de población general adulta y relacionarlas con las distintas circunstancias que se dan espontáneamente y su capacidad para identificar DSVI (ecocardiográfica).

Métodos. Se realizó un estudio cardiológico y una determinación válida de las concentraciones séricas de NTproBNP a 203 personas (entre 49 y 81 años), seleccionadas de la Comunidad Valenciana mediante un método de azar.

Resultados. La cifra promedio de NTproBNP fue de $52,2 \pm 98,2$ pmol/l. Los valores de NTproBNP variaron en razón de sexo, edad y estadio funcional (NYHA). Los más elevados coincidieron con antecedentes de edema de pulmón o con una fracción de eyección (FE) $< 40\%$. También resultaron significativamente aumentados en presencia de disnea nocturna, ortopnea, $FE \leq 50\%$, fibrilación auricular, angina y edemas maleolares. El valor de NTproBNP que mejor discriminó la $FE \leq 50\%$ fue de $37,7$ pmol/l con una sensibilidad del 92% y una especificidad del 68%.

Conclusiones. Valores elevados de NTproBNP apoyan un origen cardíaco de las manifestaciones clínicas y seleccionan pacientes para ecocardiografía. Valores bajos descartan DSVI.

Palabras clave: Insuficiencia cardíaca crónica. Péptidos natriuréticos.

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INTRODUCTION

The diagnosis of chronic congestive heart failure is based on demonstrating the cardiac reason of its clinical symptoms.¹ Fatigue, dyspnea and peripheral edema

ABBREVIATIONS

LVSD: left ventricular systolic dysfunction.

EF: ejection fraction.

NTproBNP: N-terminal brain natriuretic pro-peptide.

E/A: Transmitral pulsed-wave Doppler E/A ratio.

are its common manifestations. However these symptoms are not very specific and correlate poorly with the degree of LVSD or with prognosis. Dyspnea is the most frequent symptom and also one of the most common causes of consultation, both in primary health care and emergency wards. Echocardiographic examination is the clinical method of reference for detecting LVSD, although in primary health care echocardiographic diagnosis has an always suboptimal and variable access. A low EF is the inclusion criteria for multicentric studies and also guides prognosis and therapy. In Europe, 50 000 of every million subjects suffer dyspnea and other chronic heart failure symptoms, although presence of LVSD² will only be confirmed in 10 000 patients. In this sense, indiscriminate therapies would imply a resource mismanagement.

Natriuretic peptide plasma levels increase during heart failure in response to myocardial cells stretching.^{3,4} Atrial peptides⁵ and cerebral natriuretic peptide are produced in the ventricles and have been studied for diagnostic purposes. Their measurement reflects LVSD.^{4,6} Estimated sensitivity is 97% for in-hospital chronic heart failure diagnosis, and 76% for LVSD diagnosis. Estimated specificities are 84% and 87%, respectively.^{6,7} NTproBNP is found in higher levels than BNP, it is more stable, and has a 15 times longer half-time life.⁸⁻¹⁰

The interpretation of NTproBNP levels used in diagnostic tests depends on different clinical environments. Out-hospital population studies based on NTproBNP determinations^{6,7,11} are still scarce. We present a study of NTproBNP plasma levels in a general population randomly selected group, with the purpose of establishing the peptide levels that appear in spontaneous circumstances and defining its capacity to

identify LVSD patients. This knowledge could be useful in primary health care and for selecting echocardiographic examination patients.

METHODS

Studies population

Randomized method was used to select 203 individuals from the Valencian Community general population that accepted taking part in this study. They underwent a cardiologic examination and a valid determination of NTproBNP plasma levels. They proceeded from a sample of 10 248 individuals, 45 to 74 years old, included in the study of angina prevalence between 1995 and 1996 in Spain.¹² The original sample was stratified by gender, three age groups (45-54, 55-64, and 65-74 years) and proportional to the population of the Valencia Region.

In the Valencian Community, 999 individuals were selected,¹² and some degree of dyspnea was confirmed in 432 cases (42,8%) (Table 1). They were contacted by postal mail followed by a telephone interview between January and June, 2000. Subjects were scheduled for performing a cardiovascular examination at their nearest hospital out of a list of ten (see Appendix). As for the hospital appointment, 215 individuals presented, 131 could not be contacted, 21 had died, 6 were disabled by illness, and 59 that accepted the appointment did not show-up.

Procedures

Cardiologist examined the 215 individuals finally present at hospital. Clinical symptoms, analytical data and examination data was collected following standard protocols. The Goldman specific functional evaluation scale was applied to assess the degree of dyspnea. Pulmonary function was evaluated with a flow-meter spirometry (Boehringer Ingelheim Mini-Bell peak-flow meter), and the highest of three maximum or forced spiratory flow measurements was considered. An echocardiographic examination was performed following a predefined protocol. All echocardiographic examinations were registered on tape and sent for blind analysis to a core laboratory (see Appendix).

TABLE 1. Degree of dyspnea in 45-74 year old general population of the Valencian Community and Spain (1996)

	No dyspnea	Major stress	Mild stress	Minimum stress	Not specified
Valencian Community (n=999)	57.2%	15.6%	14.3%	2.8%	10.1%
Spain (n=10 248)	60.0%	16.9%	11.8%	5.0%	6.3%

Left ventricular EF in 2D-echo, presence of rheumatic or degenerative valvular disease, and pulsed-Doppler transmitral flow for early rapid filling velocity and late diastolic wave (E/A) ratio, were recorded. The presence of LVSD, impaired relaxation and any degree of valvular disease were also considered. Two levels were established for left ventricular dysfunction; EF <50% (used in studies of LVSD prevalence in out-hospital populations)¹³ and EF <40% (clinical level closer to multicentric study levels). An E/A <1 ratio was defined as impaired relaxation. All the patients had blood drawn and divided in two samples, for a common blood test and for measuring NTproBNP plasma levels. With this purpose, plasma was separated by 3000 rpm centrifugation for 10 min at room temperature, and the overflow was introduced in 1.5 ml Eppendorf tubes that were stored at -20°C in a freezer. Tubes were sent in this condition to the core laboratory, that performed blind analysis of the analytical determinations.

The immune-enzymatic protocol to determine NTproBNP levels was based on a MTP/ELISA⁸ technique with streptavidine sandwich supplied by Roche Diagnostics. The lowest detection limit is <3.0 pmol/L for this method.

NTproBNP levels were determined in 203 of the 215 blood extractions, as blood samples of 12 patients were not in good condition.

Statistical analysis

Data was analyzed using the SPSS 9.0 for Windows statistical software. Quantitative variables are expressed as mean standard deviation and qualitative variables are described as percentage values. The normality of quantitative variable distributions was

verified, followed by logarithmical transformation when necessary. To describe the linear association between NTproBNP levels and other quantitative variables, the Pearson correlation coefficient was used for normal distribution variables, and the Spearman correlation with non-normal variables. Mean comparison of NTproBNP levels depending on binary variables was performed using the Student t test for independent samples, or the Mann-Whitney test. The non-parametric Kruskal-Wallis test and the Jonckheere-Terpstra trend test were used for mean comparison of NTproBNP levels depending on variables with more than two categories. The χ^2 method was used for comparing categorical variables. Multiple linear regression models were created with the drug as dependent variable, and other drugs with theoretical and clinical meaningful background (potential confusion factors) as control variables. First order interactions with statistical significance were also included. The final model has a hierarchical structure, maintaining the control variables with influence on coefficients.

For evaluating the total diagnosis accuracy of NTproBNP levels in LVSD detection (defined as EF<50%), the area under the ROC curve was measured. Variable differences were considered with statistical significance when $P<.05$.

RESULTS

NTproBNP values

Group mean age (215 individuals, 98 males) was 65.9±8.9 years (interval, 49-81 years); body weight was 73.2±13 kg and height was 1.59±0.1 m. Clinical characteristics are described in Table 2.

TABLE 2. Clinical, echocardiographic and blood test manifestations of the population sample (n=215)

Clinical manifestations	(%)	Echocardiographic examinations (%)	
Dyspnea (NYHA II)	46.1	Valvular disease	27.9
Dyspnea (NYHA III)	14.6	Previous heart failure symptoms	22.2
Dyspnea (NYHA IV)	0.5	EF<40%	1.4
Nocturnal dyspnea	3.2	E/A<1	23.3
Orthopnea	4.3		
Ankle edema	11.2	Common blood test	
Muscular fatigue	19.7	Hematocrit females	41.3±3.4%
Angina	11.3	Hematocrit males	45.2±4.8%
Atrial fibrillation	2.8	Urea	38.7±16 mg/dL
History of pulmonary edema	1.1	Creatinine	1.43±1.8 mg/dL
History of arrhythmia	15.9	Potassium	4.4±0.4 mmol/L
History of syncope	10.8	CPK	96.3±51.8 UI/L
Hypertension	38.2	Maximum spiratory flow	310.1±139.8 mL/s

TABLE 3. NTproBNP values (pmol/L) depending on clinical and echocardiographic manifestations, cardiovascular risk factors, and personal history (n= 203)

	Yes	No	P
Angina	118.2±193.3	45.7±75.8	<.001
Dyspnea	69.1±126.1	41.0±67.6	<.05
Nocturnal dyspnea	169.1±243.9	50.9±91.7	<.01
Muscular fatigue	69.9±136.7	51.1±90.3	NS
Ankle edema	113.6±184.1	46.7±83.7	<.01
Orthopnea	134.1±213.5	51.1±92.5	<.05
Atrial fibrillation	131.7±65.8	43.9±88.8	<.05
EF<40%	393.6±502.7	48.8±83.0	<.001
EF<50%	150.7±200.2	45.9±82.8	<.001
E<A	56.8±99.0	37.6±85.9	NS
Valvular disease	90.0±159.1	40.8±74.1	NS
Hypercholesterolemia	61.6±124.6	46.4±68.2	NS
AHT	70.1±117.7	41.3±80.9	<.05
Diabetes	72.6±142.1	48.3±84.5	NS
Smoking, males	54.9±144.2	51.1±80.9	NS
Pulmonary edema	403.2±489.1	50.9±87.2	<.001
Syncope	73.2±128.3	49.8±93.5	NS
Arrhythmias	78.7±127.4	49.4±92.7	NS
Previous heart disease	119.3±178.8	40.6±72.7	<.01

E<A indicates altered transmittal flow E/A ratio; AHT, arterial hypertension; NS, non significant statistically.

The average NTproBNP value was 52.2 ± 98.2 pmol/L (interval, 0-749.1 pmol/L). In 90% of population considered the NTproBNP value was lower than 91.77 pmol/L. Males presented higher values than females (68.3 ± 133.9 and 39.6 ± 44.7 pmol/L, respectively; $P < .05$). Figure 1 describes the NTproBNP value and age correlation ($r = 0.49$; $P < .000$).

The highest NTproBNP levels appeared in patients with a history of pulmonary edema (403.2 ± 489 pmol/L) or with $EF < 40\%$ ($393.6 \pm 3 + 502.7$ pmol/L). Values between 169 ± 243 and 113.6 ± 184.1 pmol/L were measured in patients with nocturnal dyspnea, orthopnea, $EF < 50\%$, atrial fibrillation, history of diagnosed heart disease, chest angina or ankle edemas, in this order. Average levels in hypertensive patients were slightly above the mean value and much higher than in patients without the disease (70.1 ± 117.7 and 41.3 ± 80.9 pmol/L, respectively; $P < .05$) (Table 3).

A positive correlation was found between NTproBNP values and potassemia ($r = 0.34$; $P < .001$), uremia ($r = 0.30$; $P < .02$) and creatinine ($r = 0.20$; $P < .01$) in blood. A negative correlation was found with forced spiratory flow ($r = -0.20$; $P < .01$) and the hematocrit in males ($r = -0.28$; $P < .01$). Average NTproBNP values showed a progressive increase in the New York Heart Association functional stage ($P < .0001$).

With the aim of differentiating cardiologic profiles based on peptide plasma levels, three cut-off values

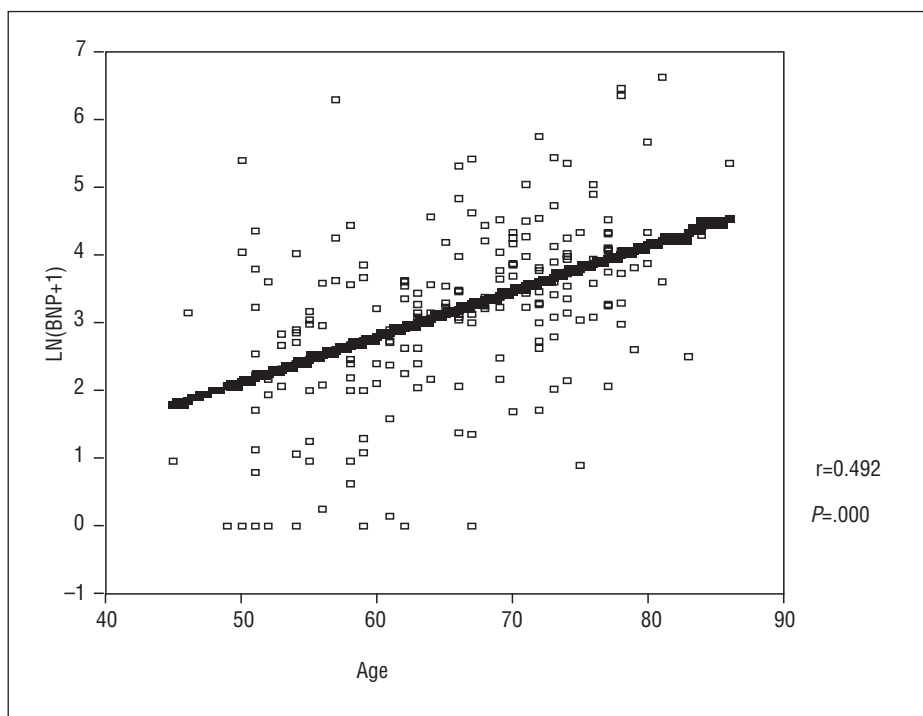


Fig. 1. Age and NTproBNP plasma values correlation (NTproBNP+1 LogN) in the 203 cases sample of considered population.

TABLE 4. Risk factors, personal history, clinical and echocardiographic manifestations depending on three NTproBNP plasma level cut-off values (n=203)

	NTproBNP ≤ 25.5 pmol/L (11.4±8.2) (n=101)	NTproBNP 25.5-210.75 pmol/L (59.5±35.4) (n=91)	NTproBNP >210.75 pmol/L (397.9±203.3) (n=10)
Hypercholesterolemia	41.6%	41.8%	50%
Arterial hypertension	25.7%	47.3% ^b	40.0%
Diabetes	16.8%	15.4%	30.0%
Smoking, males	29.8%	25.7%	25.0%
Pulmonary edema	0%	1.1%	10.0%
Syncope	6.9%	13.2%	20.0%
Arrhythmias	9.9%	19.8% ^c	30.0%
Previous heart disease	3.0%	13.2% ^a	20.0% ^a
Angina	5.9%	14.3%	30.0% ^a
Dyspnea	34.7%	48.8%	60.0%
Nocturnal dyspnea	3.0%	1.1% ^c	20.0%
Muscular fatigue	12.9%	22.0%	30.0%
Ankle edema	5.9%	11.0%	30.0% ^a
Orthopnea	2.0%	4.4%	20.0% ^a
Atrial fibrillation	0%	6.6%	0%
EF<40%	0%	1.1%	10.0%
EF<50%	1%	8.8%	30%
E<A	67.3%	85.7% ^b	80.07%
Valvular disease	7.9%	14.3%	20.0%

^aP<.05 and ^bP<.01: significant for NTproBNP<25.5 pmol/L group; ^cP<.05: significant for the NTproBNP 25.5 pmol/L to 150 pmol/L groups and NTproBNP>210.75 pmol/L group. E<A indicates altered transmitral flow E/A ratio.

were defined: equal or below the median, between median and 95 th percentile, and above the median (Table 4). Figure 2 illustrates how the cardiologic manifestation percentages increase progressively together with peptide levels.

Usefulness of NTproBNP for evaluating left ventricular function

In Figure 3, the area under the ROC curve is 0.82, indicating that NTproBNP levels in the considered population with left ventricular EF<50% will be higher than with left ventricular EF>50%, with an 82% probability.

In our group, sensitivity of <25.5 pmol/L (median) measurement for detecting normal left ventricular function (EF ≤50%) was 92% and its specificity was 53%. Similarly, we analyzed values above 210.75 pmol/L (percentile 95) for LVSD detection (EF<50%), and sensitivity was 25% while specificity was 96%.

The NTproBNP value that better discriminated EF lower and higher than 50% was 37.67 pmol/L, with 92% sensitivity and a 68% specificity. In the studied group, 64% (130 individuals) presented NTproBNP values below 37.7 pmol/L.

TABLE 5. NTproBNP values (pmol/L) depending on most frequent pharmacologic therapies

	N	NTproBNP (pmol/L)	P
ACE inh	32	51.0±96.8	NS
No ACE inh	126	79.2±137	
ACE inh+ARA II	38	90.8±168.3	.023
No ACE inh+ARA II	120	45.9±75.3	
Diuretics	19	139.5±209.8	.0001
No diuretics	139	45.4±77.9	
Betablockers agents	8	56.9±109.1	NS
No betablocking agents	150	53.0±29.0	
Digoxin	6	142.2±209.8	.045
No digoxin	152	53.3±100.1	
Calcium antagonists	34	104.8±165.0	.003
No calcium antagonists	124	43.5±79.6	

Influence of therapy on NTproBNP values

Only 76 individuals (35.3%) were not receiving any treatment. Calcium antagonists (21.3%) was the most used pharmacologic group, followed by ACE inhibitors (20.1%) and diuretics (12.4%). Patients receiving diuretics, calcium antagonists or digoxin presented significantly higher average NTproBNP values (Table 5). The differences in patients treated with ACE inhibitors were only significant if patients were con-

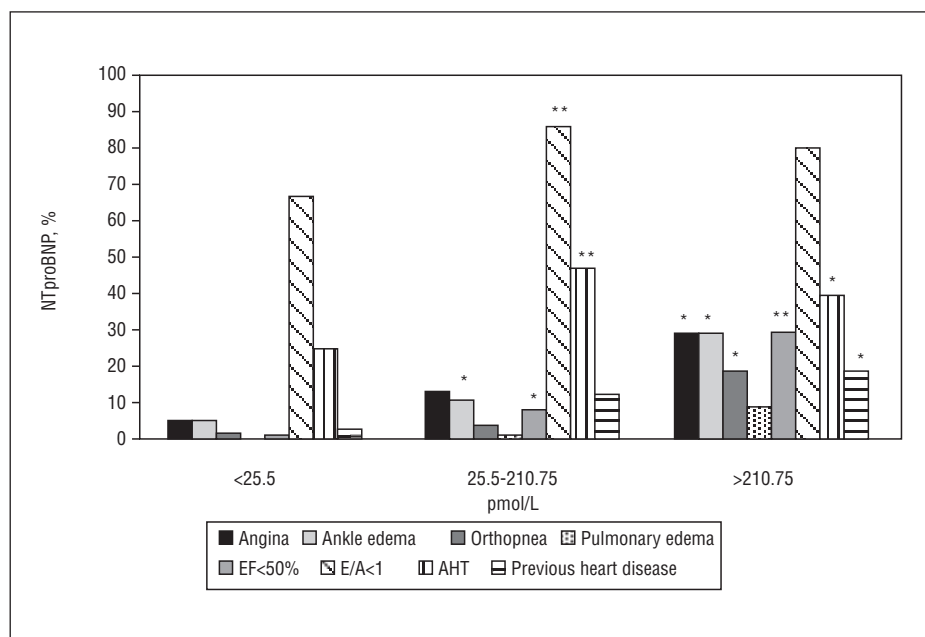


Fig. 2. Percentage of cumulative cardiovascular manifestations depending on NTproBNP values. Median, percentile 95 and above were considered.

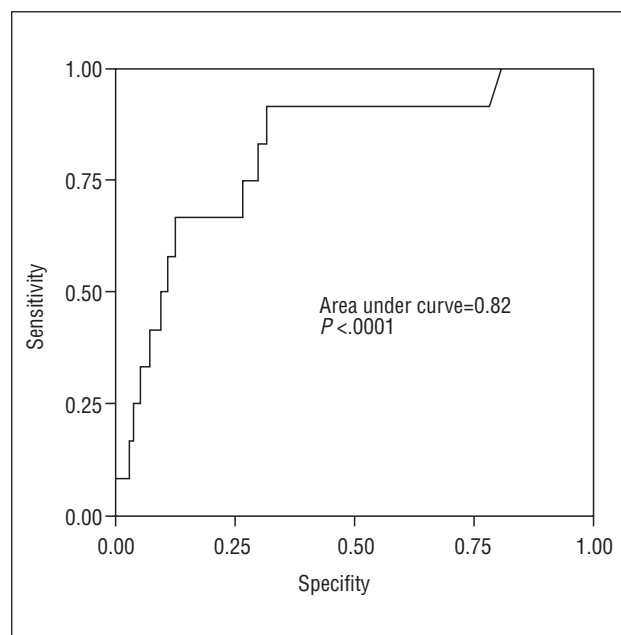


Fig. 3. ROC curve for evaluating NTproBNP capacity of LVSD detection (EF<50%) in the studied group.

sidered with the group receiving angiotensine antagonists.

As there are possibly biased effects in univariate analysis due to underlying disease, four multiple linear regression models were created with the drug as the effect variable. Absent or present dyspnea, angina, hypertension, LVSD, EF<50%, creatinine values, age and gender were the control variables. Diuretics only

increased NTproBNP levels in presence of dyspnea or angina, and calcium antagonists, in presence of dyspnea in males, or in both cases. Digoxin showed a positive effect on NTproBNP values only in males and the effect of ACE inhibitors or angiotensine antagonists depended on presence of angina and hypertension and on gender. The highest NTproBNP levels subgroup were males with angina and normal blood pressure.

DISCUSSION

Our study offers data regarding the interpretation of NTproBNP plasma levels in persons recruited outside a health care environment, but that declared some degree of exercise dyspnea. With the aim of increasing the prevalence of chronic heart failure without loss of information about the general population, we selected individuals that complained of suffering exercise dyspnea in a specific questionnaire during the PANES study. If these patients were to be examined by a cardiologist, following a functional capacity specific questionnaire, the individuals with a significant degree of dyspnea would be less than half.

Only one article with a similar aim has been found in the literature. Its population sample was patients spontaneously arriving for primary level assistance, on whom N-terminal proatrial natriuretic peptide¹⁴ levels were determined. It also emphasizes that peptide values increase noticeably with relation to age, male gender, severity of chronic heart failure manifestations, a history of heart disease, creatinine levels, presence of

edemas and atrial fibrillation. Other studies also describe renal disease^{15,16} and lung disease¹⁵ with right ventricle overload¹⁷ as causes of high NTproBNP plasma levels.

The most commonly used marker for detecting LVSD is depressed left ventricular EF. A depressed EF ($\leq 50\%$) was present in 7% of our sample, three patients had $EF \leq 40\%$ and NTproBNP values were very high, a finding in which all the authors agree.^{15,18-20} Patients with a history of acute pulmonary edema showed similar results, despite EF depression was not very high. Peptide average values were near 400 pmol/L in both circumstances. Patients with $EF \leq 50\%$, atrial fibrillation or chronic ankle edemas, a history of orthopnea and nocturnal dyspnea, or with a diagnosis of chest angina or ischemic heart disease, also showed values above 100 pmol/L. Some of these manifestations are considered very specific for the diagnosis of chronic congestive heart failure.⁷ The clinical diagnosis of chronic heart failure syndrome, in absence of confirmed LVSD at rest, is uncertain, and is not a criterion for patient inclusion in clinical trials. The diagnosis of heart failure is particularly uncertain when clinical manifestations, such as exercise dyspnea, are not very specific. Exercise dyspnea is also the most common chronic heart failure manifestation and has a 100% negative diagnosis predictive value, despite its low near 17% specificity.⁷ In this context, high NTproBNP values can increase noticeably the probability of chronic congestive heart failure.

In clinical practice, EF is used as absolute value criteria for LVSD diagnosis, although the cut-off value can be variable. Theoretically, it is a relative value for each myocardium, and a particular EF measurement could be interpreted comparatively as LVSD if baseline values were known. In other cases, LVSD is a transitory manifestation⁷ secondary to myocardial stunning with spontaneous recovery, or after bypass surgery.²¹ NTproBNP high values with a normal EF can appear in these situations.

NTproBNP levels increase mostly due to LVSD. It was myocardial dysfunction and not ischemia what determined the NTproBNP increase in patients admitted during an acute ischemic episode,^{22,23} although a significant correlation was described between ST depression during stress and increased NTproBNP levels.²⁴ In patients with ischemic heart disease and LVSD, the increased NTproBNP values dropped more than 50% 24 hours after angioplasty, and returned to normality after 14 days, depending on the degree of revascularization²⁵ (hibernated myocardium?) attained by each patient. After a myocardial infarction with is-

chemic heart disease, the segmentary disease produces NTproBNP high levels closely related to the left ventricular wall motion index.¹⁸ In our study, NTproBNP high values accompanied different ischemic manifestations, probably as a consequence of segmentary dysfunction. With atrial fibrillation, NTproBNP values and the brain and atrial natriuretic peptides⁹ increase, what is mainly determined by the ventricular function alteration that can accompany atrial arrhythmia.²⁶ Such considerations are in agreement with the high specificity for LVSD detection of NTproBNP values in our study, and can help in suspecting asymptomatic LVSD, a frequent entity in medium aged males.^{16,27,28}

In our study, values below the median showed a high sensitivity for detecting normal left ventricular function (92%). This finding is of great clinical relevance. No individual with <25 pmol/L values showed an $EF < 40\%$, had a history of pulmonary edema or presented atrial fibrillation, and patients with a history of heart disease or manifestations were less than 10%. Values slightly above median (37.7 pmol/L) represent the best cut-off point for discriminating $EF < 50\%$. As a screening test for population arriving for ambulatory medical assistance due to dyspnea, we are interested in highly sensitive BNP values (few or no false negatives) for detecting left ventricular dysfunction, at the expense of many false positives (low specificity), for applying other higher specificity tests (echocardiography) latter on.

The relation discovered in this sample between NTproBNP values and use of several drugs is influenced by other variables included, although cross-sectional studies as ours are inadequate for evaluating the effect of drugs on NTproBNP.

CONCLUSIONS

NTproBNP levels determination in the general population will not replace echocardiography for the diagnosis of chronic congestive heart failure. Elevated levels indicate an activation of cardiac adaptation mechanisms typical of chronic congestive heart failure with or without LVSD, while «normality» may reflect either absent illness or mild congestion. Elevated levels appear in patients with specific LVSD and chronic congestive heart failure manifestations, and in ischemic heart disease patients without LVSD. Patients with few or without cardiovascular manifestations and normal systolic function have peptide level values below the median. Additional tests such as echocardiographic examinations should not be indicated for these patients.

We have no scientific evidence to believe that patients selected by NTproBNP values would benefit from the pharmacologic improvements for LVSD demonstrated by clinical multicentric studies. However, elevated NTproBNP levels plus the diagnosis chronic heart failure supports that clinical symptoms are of cardiac origin and provides a physiopathological base for initiating symptomatic treatment, at least, while awaiting additional diagnostic examinations.

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Appendix. Grupo de Estudio de la Disfunción Ventricular Izquierda of the Comunidad Valenciana

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