

Usefulness of Brain Natriuretic Peptide to Evaluate Patients With Heart Failure Treated With Cardiac Resynchronization

Antonio Hernández Madrid, Mercedes Miguelañez Díaz, Carlos Escobar Cervantes, Blanca Blanco Tirados, Irene Marín, Enrique Bernal, Javier Zamora, Fernando J. Cordova González, Manuel Alfonso Pérez, Lilianna Limón, José M. González Rebollo, José L. Moya Mur, and Concepción Moro

Unidad de Arritmias, Servicio de Cardiología, Hospital Universitario Ramón y Cajal, Departamento de Medicina, Universidad de Alcalá, Madrid, Spain.

Introduction and objectives. The aim of the present study was to document the evolution of the blood levels of brain natriuretic peptide (BNP) in patients with heart failure and their correlation with the clinical course after implantation of a biventricular pacemaker.

Patients and method. Twenty-eight patients with heart failure associated to left bundle branch block and left ventricular systolic dysfunction were included in the study. In each patient we performed laboratory tests, chest X-ray, electrocardiogram and echocardiogram, and measured blood levels of BNP.

Results. During follow-up (10 [6] months) functional capacity improved, decreasing from 3.3 (0.6) to 2.10 (0.4) ($P=.03$). The rate of hospitalizations for heart failure decreased from an average of 1.8 (0.7) (6 months before the procedure) to 0.8 (0.3) (6 months after the procedure; $P=.04$). The basal value of BNP decreased from 193 (98) pg/mL to 52 (14) at the end of the follow-up in the responder group (22 patients) and increased from 564 (380) to 650 (80) pg/mL in the nonresponder group (6 patients). Patients who responded showed significant clinical improvement and decreasing levels of BNP, which reached a plateau an average of 6 months after implantation. Multivariate logistic regression analysis identified lower levels of BNP, idiopathic dilated cardiomyopathy, and functional class as independent predictors of response to therapy. Age, QRS width and left ventricular ejection fraction were not predictors of response.

Conclusions. Brain natriuretic peptide concentrations allowed us to monitor, in an objective manner, the clinical course of patients with biventricular resynchronization therapy.

Key words: *Diagnosis. Heart failure. Pacemaker.*

Full English text available at: www.revespcardiol.org

Utilidad del péptido natriurético BNP en la evaluación de pacientes con insuficiencia cardíaca tratados con resincronización cardíaca

Introducción y objetivos. El objetivo del presente estudio es establecer la evolución del péptido natriurético ventricular o tipo B (BNP) y su correlación con la evolución clínica de pacientes con insuficiencia cardíaca tras el implante de un sistema de estimulación biventricular.

Pacientes y método. Se incluyó a 28 pacientes con insuficiencia cardíaca asociada a trastorno de la conducción intraventricular y disfunción sistólica ventricular. Los pacientes fueron sometidos a una valoración previa que incluía analítica, radiografía de tórax, electrocardiograma, ecocardiograma y concentraciones de BNP.

Resultados. Durante el seguimiento, de 10 ± 6 meses, la capacidad funcional mejoró de $3,3 \pm 0,6$ a $2,10 \pm 0,4$ ($p = 0,03$). La tasa de hospitalizaciones por insuficiencia cardíaca disminuyó desde $1,8 \pm 0,7$ ingresos 6 meses antes del implante a $0,8 \pm 0,3$ ingresos 6 meses tras el implante ($p = 0,04$). Los valores basales de BNP disminuyeron de 193 ± 98 a 52 ± 14 pg/ml al final del seguimiento en el grupo de pacientes con respuesta (22 pacientes), y aumentó de 564 ± 380 a 650 ± 80 pg/ml en el grupo de pacientes sin respuesta (6 pacientes). Los pacientes con respuesta a la terapia presentaron una mejoría clínica significativa y una reducción de los valores de BNP, con una meseta a los 6 meses del implante. El análisis de regresión logística multivariable identificó como predictores de respuesta la presencia de miocardiopatía idiopática, una clase funcional distinta de

SEE EDITORIAL ON PAGES 279-82

This work was funded by a research grant from Schering España.

Correspondence: Dra. C. Moro.
Unidad de Arritmias. Servicio de Cardiología. Hospital Ramón y Cajal.
Carretera de Colmenar, Km 9,100. 28034 Madrid. España.
E-mail: cmoro.hrc@salud.madrid.org

Received 30 July, 2003.

Accepted for publication 29 January, 2004.

ABBREVIATIONS

BNP: brain or type B natriuretic peptide.
LVEF: left ventricular ejection fraction.
ACEI: angiotensin converting enzyme inhibitors
ARA-II: angiotensin II receptor antagonists.
NYHA: New York Heart Association.

la IV y valores de BNP menores. La edad, la duración del complejo QRS y la fracción de eyección ventricular izquierda basal no fueron predictores de respuesta significativos.

Conclusiones. La determinación del péptido natriurético permite controlar de una forma objetiva la evolución clínica de los pacientes con estimulación biventricular.

Palabras clave: *Diagnóstico. Insuficiencia cardíaca. Marcapasos.*

INTRODUCTION

The incidence and prevalence of patients with heart failure are increasing with the aging population. Despite the optimization of medical treatment with adequate combined therapy [angiotensin converting enzyme inhibitors (ACEI), beta-blockers, diuretics, and digoxin, etc], the quality of life and prognosis of patients with heart failure remains poor. In the last 20 years, the pathophysiology and treatment of heart failure have focused on the function and hemodynamics of the left ventricle and on ventricular remodeling. Delay in the electrical activation of the left ventricle and bundle branch block (commonly seen in patients with heart failure) have a negative effect on ventricular function due to asynchrony in the contraction of the myocardium—a result of the correlation between the duration of the QRS complex and ventricular function.¹ Biventricular cardiac stimulation or cardiac resynchronization has beneficial effects in patients with heart failure such as increased tolerance to exercise and an improvement in symptoms and functional class. Furthermore, the number of admissions due to decompensation in patients with advanced heart failure and left ventricular systolic dysfunction is reduced.^{2,3}

It has recently been shown that patients with heart failure have high levels of brain or type B natriuretic

peptide (BNP), and that there is a correlation between these and the severity of their condition.⁴ Many studies report that monitoring BNP levels could be a sensitive⁵ method for diagnosing heart failure⁶⁻⁸ and performing risk stratification,⁹ and that they could act as an independent predictor of adverse events helping clinicians arrive at a prognosis.¹⁰ The aim of the present study was to analyze the changes in serum BNP levels and to examine their correlation with the clinical course of heart failure patients treated with cardiac resynchronization.

PATIENTS AND METHODS

The 28 consecutive patients of this study had been referred to the arrhythmia department because of clinical heart failure associated with an intraventricular conduction disorder (left bundle branch block or non-specific intraventricular conduction disorder with a QRS complex of >140 ms). For inclusion, all patients had to fall into New York Heart Association (NYHA) classes III-IV, have a dilated cardiomyopathy of any etiology but with reduced left ventricular systolic function (left ventricular ejection fraction [LVEF]<40%), and show either sinus rhythm or atrial fibrillation. All patients had to be stable in terms of their functional class at entry. Patients with acute decompensation likely to improve with specific treatment were excluded.

Implantation Protocol

Before implanting the biventricular stimulation device, all patients underwent an examination that included basic blood analysis, a chest x-ray, a 12-lead electrocardiogram, an echocardiogram (2-dimensional M mode), echo, and color Doppler (with special evaluation of left ventricular function, ventricular contraction asynchrony and ventricular filling pattern) and a 6-minute walking test. Serum BNP levels were also recorded. All patients gave their signed, informed consent to be included.

An electrode was placed at the apex of the right ventricle. An inductor was then placed inside the coronary sinus, and a balloon catheter introduced for angiography and to evaluate the anatomy of the sinus and its branches. Once the subsidiary veins were identified, the electrode was introduced and set in place. In all patients, the electrode was implanted in a lateral or postero-lateral vein. If an implantable automatic defibrillator was indicated, a generator with this function was provided. Adequate stimulation by the pacemaker was tested and baseline variables were checked to ensure they were acceptable for biventricular stimulation. On release from hospital, the stimulation system was checked to confirm biventricular capture: function was normal

in all patients. The mean threshold for the left ventricle was 1.42 mV. Patients continued with the optimized medication they had received for at least one month before the implantation procedure. Stimulation variables were optimized in all patients by echocardiography before release to ensure adequate ventricular resynchronization and to program the optimum atrioventricular interval. Patients with ventricular arrhythmias or with MADIT-II criteria were implanted with an automatic defibrillator.

Patient Assessment and Follow-Up

Patients were followed up through a series of programmed revisions at 3, 6, 12, and 18 months. They were also seen if there was a deterioration in their clinical condition. During these visits, medical histories were updated and the patients underwent a physical examination, the clinical determination of their NYHA functional class, a 12-lead electrocardiogram and a radioventriculographic study of their LVEF. In addition, serum BNP levels were determined and pacemaker programming was checked. If patients showed clinical deterioration, a new echocardiographic study was performed to achieve optimization.

At 6 months, those patients who survived and showed an improvement of at least 10% in the distance they could walk during the 6-minute walking test (i.e., compared to baseline) were defined as responders. Non-responders were defined as those who experienced no benefit from the therapy or whose condition worsened (those who showed no increase in exercise tolerance, who needed a heart transplant, or who died from persistent, progressive heart failure).

Brain natriuretic peptide levels were determined using an immunoradiometric analysis kit (Shionogi and Co., Osaka, Japan) following the manufacturer's recommendations. The normal mean concentration for BNP (18.4 pg/mL; detection limits 2.5 pg/mL) was used as a reference in the evaluation of results.

Statistical Analysis

Data are expressed as means \pm standard deviation for continuous variables, and as frequencies for categorical variables. During follow-up, the Student *t* test was used to compare the means of quantitative variables with normal distribution. Qualitative variables were compared using the χ^2 test. Pearson's correlation coefficient was calculated to determine the linear association between BNP levels and other quantitative variables with normal distribution. Multivariate logistic regression was used to determine the clinical predictors of response to therapy. Significance was set at $P < .05$.

TABLE 1. Patient Baseline Clinical Data*

Variable	Data (n=28)
Age, years	66 \pm 9
Sex, male/female	21/7
Cardiomyopathy	17 idiopathic dilated, 11 ischemic
Duration QRS, ms	168 \pm 23
Atrial fibrillation, n (%)	8 permanent (29)
Ventricular arrhythmia, n (%)	8 (29)
Defibrillator, n (%)	12 (42)
Dimension left atrium, mm	49 \pm 7
Mitral regurgitation, grade 1-4	1.7 \pm 0.7
End-diastolic ventricular diameter, mm	71 \pm 9
End-systolic ventricular diameter, mm	54 \pm 7
Left ventricular ejection fraction	30 \pm 8%
NYHA functional class	3.3 \pm 0.6
Distance walked in 6 min, m	262 \pm 33
Systolic blood pressure, mm Hg	125 \pm 16
Diastolic blood pressure, mm Hg	82 \pm 5
Heart rate, lat/min	83 \pm 9
Digoxin, n	20
Diuretics, n	28
ACEI/ARA-II, n/n	23/3
Beta-blockers, n	23
Spironolactone, n	8

*NYHA indicates New York Heart Association; ACEI, angiotensin converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists.

RESULTS

Clinical and Implant Characteristics

Of the 28 patients studied, 21 were men and 7 were women. Mean age at the time of implantation was 66 \pm 9 years (range, 51-83 years). The mean total duration of the implantation procedure was 123 \pm 33 min (range, 45-220 min); the mean time taken to implant the probe in the coronary sinus was 36 \pm 14 min (range, 5-115 min). Mean investigation time was 32 \pm 18 min.

Table 1 shows the patients' baseline clinical data. Seventeen patients (61%) showed idiopathic dilated cardiomyopathy, and 11 (39%) showed dilated cardiomyopathy induced by chronic ischemia. Before implantation, the electrocardiograms of 20 patients demonstrated sinus rhythm; the remaining 8 showed permanent atrial fibrillation. The mean duration of the QRS complex was 168 \pm 23 ms. Eight patients had previously presented with malignant ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation). Twelve patients were implanted with a defibrillator with biventricular stimulation capacity. The mean LVEF measured by echocardiography prior

TABLE 2. Characteristics of Responders and Non-Responders*

Variable	Response (n=22)	No Response (n=6)	P
Age, years	66±6	66±7	NS
Sex, male/female	16/5	6/2	NS
Cardiomyopathy	15 dilated, 7 ischemia	2 dilated, 4 ischemic	.01
Defibrillator, n (%)	9 (41)	3 (50)	NS
NYHA functional class	3.2±0.6	3.6±0.4	NS
Duration of QRS pre-implantation, ms	167±20	172±21	NS
Permanent atrial fibrillation, n (%)	5 (23)	3 (50)	NS
LVEF baseline echocardiography, %	31±0.7	26±10	NS
LVEF final echocardiography, %	39±4	30±2	.01
Distance walked in 6 minutes at baseline, m	282±32	187±43	.03
Distance walked in 6 minutes at end of follow-up, m	354±32	265±41	.04
Pre-implantation medication			
Digoxin, n (%)	16 (72)	4 (66)	
Diuretics, n (%)	22 (100)	6 (100)	
ACEI/ARA-II, n (%)	21 (95)	5 (83)	
Beta-blockers, n (%)	18 (82)	5 (83)	
Spironolactone, n (%)	5 (23)	3 (50)	
Post-implantation medication			
Digoxin, n (%)	11 (50)	5 (83)	
Diuretics, n (%)	17 (77)	6 (100)	
ACEI/ARA-II, n (%)	21 (95)	5 (83)	
Beta-blockers, n (%)	18 (82)	4 (66)	
Spironolactone, n (%)	1 (4)	4 (66)	
BNP baseline, pg/mL	193±98	564±380	.01
BNP final, pg/mL	52±14	650±80	.01

*LVEF indicates left ventricular ejection fraction; ACEI, angiotensin converting enzyme inhibitors; ARA-II, angiotensin II receptor antagonists; BNP, brain natriuretic peptide.

to implantation was 30±8%. As shown in Table 1, pharmacological treatment was optimized in all patients who tolerated medication for heart failure. No significant differences were seen in baseline tolerance to exercise between eventual responders and non-responders to resynchronization treatment. At the end of follow-up, those who responded positively required fewer diuretics and less digoxin for the control of their symptoms.

Association Between Clinical Course and BNP Levels

Over a period of 10±6 months following the implantation of the biventricular stimulation system, the patients as a whole experienced an improvement in their tolerance to exercise as determined by the distance covered in the 6-minute walking test (262±33 m at baseline compared to 318±65 m at the end of follow-up; $P=.04$), and in terms of LVEF (30±8 compared to 36±8%; $P=.03$). Functional capacity improved from NYHA functional class 3.3±0.6 to 2.10±0.4 ($P=.03$). Admission to hospital for heart failure was reduced from a mean of 1.8±0.7 hospitalizations 6 months before implantation to

0.8±0.3 6 months after implantation ($P=.04$). Two patients died during follow-up (one at 4 and one at 24 months after implantation) due to persistent heart failure; one of these patients suffered arrhythmic storm. The patient who died at 4 months showed no changes in BNP values, whereas the patient who died later showed a maintained reduction in serum BNP levels until final decompensation.

The 22 responders experienced progressive reductions in their BNP levels during follow-up, while those who showed no benefit from biventricular stimulation (either at 1 month or later [n=6]), showed either stable or increasingly high BNP levels (Table 2 and Figure). Among the responders, BNP levels fell from 193±98 pg/mL to 52±14 pg/mL at the end of follow up, whereas in non-responders they increased from 564±380 pg/mL to 650±80 pg/mL. BNP concentrations fell over the follow-up period, only becoming stable 6 months after receipt of the implant.

Table 2 shows there were no significant differences between responders and non-responders in terms of age, sex, the duration of the QRS complex, LVEF, or the presence of atrial fibrillation. However, this result should be taken with care given the small size of the

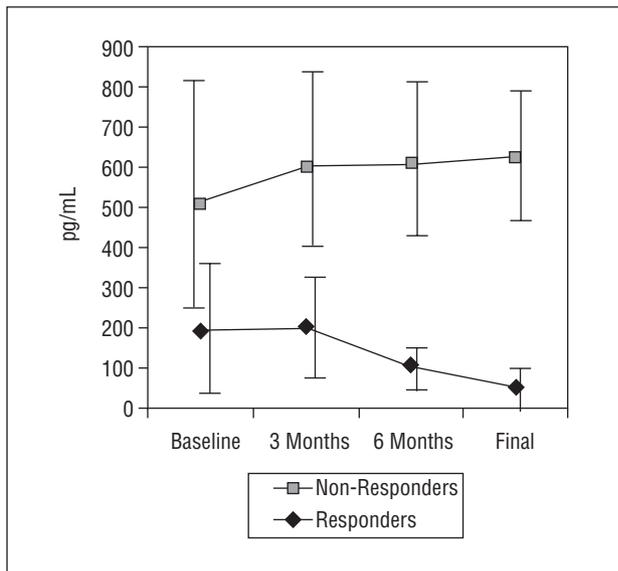


Fig. 1. Change in BNP following implantation of a biventricular stimulation system—responders and non-responders.

sample. For example, even though 50% of non-responders and only 23% of responders showed atrial fibrillation, these figures were not significantly different.

The baseline BNP levels of the non-responders were higher than those of the responders.

The Pearson correlation analysis showed no relationships to exist between BNP levels and any other variable: for example, the correlation between baseline LVEF (determined echocardiographically) and baseline BNP levels was $r=0.16$. Nor was any relationship seen between baseline LVEF and the improvement seen in BNP levels at the end of follow-up ($R=0.26$). The QRS interval was not related to baseline BNP levels ($r=-0.02$) nor to those at the end of follow-up ($r=0.14$). Due to the sample size, it is difficult to state a cut-off value that establishes with reasonable certainty what the response to resynchronization therapy might be, but ROC curve analysis suggested this to be 300 pg/mL.

Predictors of Response to Cardiac Resynchronization Therapy

Univariate analysis showed that responders had idiopathic dilated cardiomyopathy more often than ischemic heart disease, and fell into a functional class of <IV. Non-responders had higher BNP levels and showed a lower baseline tolerance to exercise in the

6-minute walking test. However, no difference was seen between responders and non-responders in terms of baseline LVEF ($26\pm 9\%$ in responders and $31\pm 7\%$ in non-responders; $P=.10$), the duration of the baseline QRS complex (172 ± 24 in responders compared to 167 ± 20 in non-responders; $P=.32$), or age. To determine the independent power of BNP levels to predict response to therapy, multivariate analysis was performed using logistic regression. Low BNP levels, the presence of idiopathic dilated cardiomyopathy and a functional class less than IV were all predictors of a positive response. Neither LVEF nor the duration of the QRS complex (which were negatively correlated $r=-0.54$; $P=.01$) were related to response to therapy or baseline BNP levels.

DISCUSSION

The results show that after implantation of a device providing biventricular stimulation, functional improvement occurs in many patients with persistent heart failure and left bundle branch block. However, candidates for this procedure must be properly selected since some improve greatly whereas others do not do so well. In the majority of previous studies, functional improvement was assessed subjectively; this is one of the first to analyze levels of a new biochemical marker of heart failure—BNP.

Since the earliest observations in 1983, many studies have reported that biventricular stimulation, which corrects asynchrony in ventricular contraction, notably increases cardiac output and systolic blood pressure, reduces pulmonary capillary blood pressure, and improves left ventricular systolic function. Controlled studies such as the PATH-CHF, MUSTIC, and MIRACLE^{2,11-13} trials have shown it to lead to an improvement in exercise capacity, quality of life, an increase in oxygen consumption, and a reduction in the number of hospital admissions and days spent in hospital. The MUSTIC trial showed that the benefits obtained at 6 months were maintained at one year.

Brain natriuretic peptide is produced almost exclusively in the heart.^{14,15} It is released in response to excess salt and water retention, cavity dilation, increased end-diastolic pressure, and to an increase in atrial and ventricular volume and stress. Since natriuretic peptides reliably reflect the pressure of cardiac filling and parietal stress, the monitoring of plasma concentrations allows the condition of a patient to be followed. An increasing number of studies are showing that natriuretic peptide levels should be used in the diagnosis of congestive heart disease since they provide information on the degree of deterioration of ventricular function. They also help determine functional class, are useful in risk stratification, and help predict events such as sudden

death in patients with cardiomyopathy (especially among the elderly and among those who have suffered a heart attack or who have advanced heart failure). It has also been observed that BNP levels measured at regular intervals allow the identification of decompensated patients who are most likely to be readmitted after release. It has been shown that the drugs that reduce left ventricular parietal stress, such as ACEI, beta-blockers, spironolactone and diuretics, reduce plasma levels of natriuretic peptides. The present work shows that, by reinstating cardiac synchrony, biventricular stimulation leads to a significant reduction in BNP levels in patients with advanced heart failure who were receiving optimal medical treatment before implantation. This finding increases the hope of being able to use BNP as an ideal biochemical marker for orientating therapy and determining prognoses. Figure 1 shows that the BNP levels of the present responders became progressively lower, reaching a plateau at 6 months. The remodeling of the ventricle that occurs after resynchronization requires months rather than minutes for maximum therapeutic benefit to be obtained. In a recent paper it has been reported that BNP levels reflect the degree of reversion of left ventricle remodeling, thus demonstrating the effectiveness of cardiac resynchronization.¹⁶

Cardiac resynchronization has been found effective in 75%-80% of patients included in controlled studies,^{17,18} similar to that seen in the present work. Patients who are candidates for this procedure should therefore be selected very carefully. However, it should be taken into account that the criteria used to define a positive response to cardiac resynchronization therapy vary between studies. Some have defined responders as those who survive and whose symptoms improve (i.e., those whose functional class designation improves by at least one grade), or whose tolerance to exercise improves and who show a 10% increase in oxygen consumption. Others have defined responders as those whose left ventricular systolic volume undergoes a reduction of >15%. Non-responders have been defined as those who show no reduction (or an increase) in functional class, who score no better on specific quality of life tests, or who require a heart transplant or die through persistent heart failure.

The majority of studies have recorded no significant differences in baseline QRS between responders and non-responders. The PATH-CHF¹¹, MUSTIC SR,² and MIRACLE¹³ trials showed that therapy is effective in patients with sinus rhythm—hence its inclusion in the latest treatment guides.¹² Some studies have shown it to be effective in patients with permanent atrial fibrillation.

The importance of ventricular asynchrony is being increasingly recognized, and new echocardiographic criteria are under study, including tissue Doppler

studies. In the present study, patients with dilated cardiomyopathy showed lower BNP levels than those with chronic ischemic heart disease. In fact, nearly all our patients with idiopathic dilated cardiomyopathy responded to treatment.

CONCLUSIONS

Brain natriuretic peptide allows the clinical course of patients treated with biventricular resynchronization therapy to be objectively monitored.

REFERENCES

1. Murkofsky RL, Dangas G, Diamond JA, Mehta D, Schaffer A, Ambrose JA. A prolonged QRS duration on surface electrocardiogram is a specific indicator of left ventricular dysfunction. *J Am Coll Cardiol* 1998;32:476-82.
2. Cazeau S, Leclercq C, Lavergne T, Walker S, Varma C, Linde C, et al. Effects on multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;12:873-80.
3. Leclercq Ch, Kass D. Retiming the failing heart: principles and current clinical status of cardiac resynchronization. *J Am Coll Cardiol* 2002;39:194-201.
4. Osca J, Quesada A, Arnau M, Osa A, Hervas I, Almenar L, et al. Péptido cerebral natriurético. Valor diagnóstico en la insuficiencia cardíaca. *Rev Esp Cardiol* 2002;55:7-15.
5. Tsutamoto T, Wada A, Maeda K, Hisanaga T, Maeda Y, Fukui D, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure. *Circulation* 1997;96: 509-16.
6. Dao Q, Krishnaswamy P, Kazanegra R, Harrison A, Amirnovin R, Lenert L, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent care setting. *J Am Coll Cardiol* 2001;37:379-85.
7. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;3:161-7.
8. McCullough P, Nowak RM, McCord J, Hollander JE, Herrmann HC, Steg PG, et al. B-type natriuretic peptide and clinical judgment in emergency diagnosis of heart failure. Analysis from Breathing Not Properly (BNP) Multinational Study. *Circulation* 2002;106:416-22.
9. Koglin J, Pehlivanli S, Schwaiblmair M, Vogeser M, Cremer P, von Scheidt W, et al. Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. *J Am Coll Cardiol* 2001;38:1934-41.
10. Maisel A. B-Type natriuretic peptide levels: diagnostic and prognostic in congestive heart failure. What's next? *Circulation* 2002; 105:2328-31.
11. Auricchio A, Stellbrink C, Sack S, Block M, Vogt J, Bakker P, et al. Chronic benefit as a result of pacing in congestive heart failure: results of the Path CHF trial. *J Cardiac Fail* 1999;5:1-78.
12. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, et al. ACC/AHA/NASPE 2002 guidelines update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article. *Circulation* 2002;106: 2145-61.
13. Abraham W, Fisher W, Smith A, Delurgio DB, Leon AR, Loh E, et al. Cardiac resynchronization in chronic heart failure. *N*

- Engl J Med 2002;346:1845-53.
14. Clerico A, del Ry S, Maffei S, Prossiter C, Emdin M, Giannessi D. The circulating levels of cardiac natriuretic hormones in healthy adults: effects of age and sex. *Clin Chem Lab Med* 2002; 40:371-7.
 15. Cosin J, Hernández A, Díez J, Capdevila C, Salvador A, Diago J. Valor del nivel de NT pro BNP en población adulta extrahospitalaria. *Rev Esp Cardiol* 2003;56:236-44.
 16. Sinha A, Filzmaier K, Breithardt O, Kunz D, Graf J, Markus K, et al. Usefulness of brain natriuretic peptide release as a surrogate marker of the efficacy of long-term cardiac resynchronization therapy in patients with heart failure. *Am J Cardiol* 2003; 91:755-7.
 17. García Bolao I, Macías A, Alegría E, Berenguell A, Gavira J, Azcárate P. Tratamiento de la insuficiencia cardíaca avanzada mediante estimulación biventricular. Experiencia inicial en una serie de 22 casos consecutivos. *Rev Esp Cardiol* 2003;56:245-52.
 18. Leon A, Greenberg J, Kanuru N, Baker CM, Mera FV, Smith AL, et al. Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation. *J Am Coll Cardiol* 2002;39: 1258-63.