



## Original Article

## Usefulness of the N-Terminal Fraction of Brain Natriuretic Peptide for Deciding When to Refer Patients With Sleep Apnea-Hypopnea Syndrome to the Cardiologist

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## ABSTRACT

**Introduction and objective:** When sleep apnea-hypopnea syndrome (SAHS) and cardiovascular disease occur concurrently, prognosis is affected. Echocardiography can detect structural cardiac abnormalities but using this technique in all patients would place a heavy burden on resources. The objective of this study was to investigate whether the N-terminal fraction of brain natriuretic peptide (NT-proBNP) can be used as a marker for silent heart disease.

**Patients and methods:** NT-proBNP concentration was measured in the 114 consecutive patients with SAHS who underwent echocardiography before starting treatment. Left and right ventricular systolic and diastolic function, as well as structural abnormalities, were studied. Correlations between NT-proBNP concentration and the abnormalities detected were investigated. A receiver operating characteristics (ROC) curve was plotted for NT-proBNP concentration and cardiac abnormalities.

**Results:** Data for 98 patients were finally analyzed. NT-proBNP concentration was significantly correlated with ventricular septal thickness ( $r=0.63$ ), posterior wall thickness ( $r=0.45$ ), and left ventricular end-diastolic diameter ( $r=0.51$ ) ( $P<.0001$  for all correlations). The area under the ROC curve was significant (0.870; 95% confidence interval, 0.801-0.939;  $P<.0001$ ). Assuming that specificity would be more useful for clinical practice, we calculated that NT-proBNP concentrations below 100 and 200 pg/mL could rule out structural abnormalities with a reliability of 90% and 100%, respectively.

**Conclusions:** NT-proBNP concentration was strongly correlated with echocardiographic abnormalities and so could be a useful tool for identifying patients who should be referred to the cardiologist.

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## ¿Cuándo remitir al cardiólogo al paciente con síndrome de apneas-hipopneas durante el sueño? Utilidad del NT-proBNP

## RESUMEN

## Palabras clave:

Síndrome de apneas-hipopneas durante el sueño

Ecocardiografía Doppler

Péptidos natriuréticos

**Introducción y objetivo:** La comorbilidad cardiovascular del síndrome de apneas-hipopneas durante el sueño (SAHS) condiciona su pronóstico. La ecocardiografía detecta alteraciones estructurales, pero realizarla a todos los pacientes ocasionaría un gran consumo de recursos. El objetivo de este trabajo ha sido estudiar el papel de la fracción N-terminal del péptido natriurético cerebral (NT-proBNP) para detectar cardiopatía silente.

**Pacientes y métodos:** Se seleccionó a 114 pacientes consecutivos con SAHS, a quienes se les determinó la concentración de NT-proBNP y se les realizó una ecocardiografía antes de que recibieran tratamiento. Se estudiaron las funciones sistólica y diastólica de ambos ventrículos, así como las alteraciones morfológicas. Se analizaron las correlaciones existentes entre el NT-proBNP y las alteraciones halladas. Se realizó una curva de eficacia diagnóstica entre el NT-proBNP y la presencia de alteración cardíaca.

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**Resultados:** Finalmente se estudió a 98 pacientes. El NT-proBNP se correlacionó de forma significativa ( $p < 0,0001$ ) con el grosor del tabique interventricular ( $r = 0,63$ ), con el de la pared posterior ( $r = 0,45$ ) y con el diámetro telediastólico del ventrículo izquierdo ( $r = 0,51$ ). La curva de eficacia diagnóstica calculó un área bajo la curva significativa (0,870; intervalo de confianza del 95%, 0,801-0,939;  $p < 0,0001$ ). Se consideró más útil para la práctica clínica el valor de especificidad. Así, unos valores de NT-proBNP inferiores a 100 y 200 pg/ml descartan que haya alteraciones morfológicas cardíacas con una fiabilidad del 90 y el 100%, respectivamente.

**Conclusiones:** El NT-proBNP tiene correlaciones relevantes con la presencia de alteraciones ecocardiográficas y podría ser una herramienta útil para identificar a los pacientes que deberían ser remitidos para estudio cardiológico.

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## Introduction

The prevalence of sleep apnea-hypopnea syndrome (SAHS) is high and increases with age.<sup>1,2</sup> It affects between 4% and 6% of middle-aged men and 2% and 4% of middle-aged women. Defined as excessive daytime sleepiness and cognitive-behavioral, respiratory, cardiac, or inflammatory disorders arising from repeated episodes of upper airway obstruction during sleep, the disease can cause to cardiac disorders with high associated morbidity and much worse prognosis.<sup>3-5</sup>

Doppler echocardiography, available in nearly all hospitals, is a noninvasive, harmless, inexpensive, reproducible technique. These characteristics make it the technique of choice for detecting structural abnormalities in patients with SAHS. However, there is a backlog of patients awaiting echocardiography in many hospitals, and in view of the high prevalence of SAHS, cardiology departments currently seem to be unable to undertake this examination in these patients.

The N-terminal fragment of brain natriuretic peptide (NT-proBNP) has proven a useful biomarker of systolic and diastolic myocardial dysfunction. The concentration of NT-proBNP is elevated in situations of cardiac overload and this substance is used in cardiology as a marker for screening for heart disease, for diagnosis and prognosis, and to monitor the effects of therapy in heart failure.<sup>6</sup>

The hypothesis of this study was that NT-proBNP could help identify those patients with SAHS who might have cardiac abnormalities worthy of assessment by the cardiology department. This would allow early treatment of those abnormalities and/or SAHS. The objective of this study was therefore to analyze the plasma concentration of NT-proBNP at the time of diagnosis in a series of patients with SAHS and to determine the ability of this peptide to distinguish patients with cardiac abnormalities identified by echocardiography.

## Patients and Methods

### Patients

The study included 114 consecutive patients who were referred for specialist assessment of sleep-disordered breathing and who were subsequently diagnosed with SAHS. These patients were informed of the characteristics of the study and consented to their participation. The study was approved by the ethics committee of the hospital.

### Sleep Study

SAHS was diagnosed by respiratory polygraphy using the Embletta polygraph (Flaga, Reykjavik, Iceland), which has been validated against conventional polysomnography.<sup>7</sup> Nasal flow was recorded with a pressure transducer, oxygen saturation and heart rate with a digital pulse oximeter, snoring and number of apneas according to

the position of the patient with a body position sensor, and thoracoabdominal movements with an elastic belt equipped with a piezoelectric sensor and fastened around the chest or abdomen. All studies were scored manually by the same pulmonologist. When the symptoms were very indicative of diagnosis but respiratory polygraphy was considered negative for SAHS, the patient was referred to a sleep unit for conventional polysomnography.<sup>8</sup>

Obstructive apnea was defined as the absence of a respiratory signal or a reduction by more than 90% for more than 10 seconds, in the presence of respiratory effort detected by the elastic belts. Central apnea was defined as the absence of a respiratory signal or reduction by more than 90% for more than 10 seconds with no respiratory effort detected by the elastic belts. Mixed apnea was considered to occur when the respiratory event would start with a central component and end with an obstructive one. Hypopnea was defined as a discernible reduction (>30% and <90%) in the respiratory signal for more than 10 seconds, detected by thermistors, nasal pressure cannulas, or pneumotachography, accompanied by desaturation (>3%) and/or arousals in the electroencephalogram recorded by polysomnography. In the case of respiratory polygraphy, the apnea-hypopnea index (AHI) was defined as the number of respiratory events (apneas or hypopneas) detected per hour of recording in bed.<sup>8</sup> Studies were considered valid when the patients reported having slept almost normally for at least 4 hours and invalid when this was not the case or the sensors had become disconnected. A diagnosis of SAHS was established by an AHI of 10 or more, with or without excessive daytime sleepiness (Epworth score >10). Continuous positive airway pressure (CPAP) treatment was indicated when the AHI was 30 or more, or when it was 10 or more and accompanied by other factors, such as excessive daytime sleepiness, cardiovascular risk factors, or confirmed vascular disease.<sup>8</sup>

### Echocardiographic Study

All patients underwent a Doppler echocardiographic examination using an HP Sonos 5500 device with a 2.5 MHz probe (Philips, Eindhoven, Netherlands). All examinations were performed by the same person, who was unaware of the patient's NT-proBNP concentration and severity of SAHS.

Structural measurements were done in M mode in the long-axis parasternal view. The ejection fraction was calculated from these measurements using the Teicholz method. Diastolic function was investigated using pulsed Doppler images between the edges of the mitral valve in an apical 4-chamber view. Aortic flow was measured in the aortic valve plane.

The following variables were recorded:

1. Structural variables: Right ventricular end-diastolic diameter (EDD), ventricular septal thickness (VST), and left ventricular posterior wall thickness, which define left ventricular hypertrophy, plus left ventricular diameter, left ventricular EDD, and end-

systolic diameter, which provide information on heart size. A VST greater than 12 mm and a left ventricular EDD greater than 56 mm were considered abnormal.

2. Systolic function parameters: Left ventricular ejection fraction and right ventricular function estimated visually. Left ventricular systolic function was considered to have diminished when the ejection fraction was less than 50%. Decreased right ventricular systolic function was defined as less-than-normal contractility.
3. Diastolic function parameters: Early (E wave) and late (A wave) diastolic mitral filling and isovolumetric relaxation time, which define the normal and abnormal ventricular filling patterns.

Each value recorded was the mean of 3 measurements. These 3 measurements were used to calculate the intraobserver variability, which was 1.8% in the case of structural and systolic function variables and 0.9% in the case of diastolic function variables. Agreement ( $\kappa$ ) was greater than 0.8 in all cases.

#### Study Design and Inclusion and Exclusion Criteria

Patients were included consecutively in the study before starting treatment with CPAP. All patients underwent measurement of NT-proBNP plasma concentration and echocardiography.

Excluded were patients who did not give their informed consent; those who had been treated previously with CPAP; and those with atrial fibrillation, bradyarrhythmia (<60 beats/min), or tachyarrhythmias (>100 beats/min), prior documented heart disease or valve disease detected during the examination, chronic obstructive pulmonary disease more severe than stage I according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification,<sup>8</sup> or chronic cor pulmonale of any other etiology.

Patients were defined as having hypertension if they were taking antihypertensive medication or had blood pressure greater than 140/90 mmHg in 3 morning measurements taken by the same experienced nurse.<sup>9</sup> All smokers were screened for chronic obstructive pulmonary disease by spirometry with a bronchodilator test, in accordance with GOLD recommendations and were assigned GOLD severity classes.<sup>10</sup>

#### Technique for Measuring NT-proBNP

Qualified staff extracted venous blood samples after overnight rest and at least 30 minutes lying in bed but before oral intake of food or medication. NT-proBNP levels were analyzed by chemoluminescence with the Elecsys proBNP system (Roche Diagnostics, Mannheim, Germany).

#### Statistical Analysis

Continuous variables were expressed as means (SD) and categorical ones as percentages. The Kolmogorov-Smirnov test was applied to check for normal distribution. Variables that were not normally distributed were expressed as medians and interquartile range. Correlations between nonparametric variables were assessed using the Spearman  $\rho$  test. The Pearson correlation coefficient was used for variables with a normal distribution. Plots for linear and squared correlations were made and the corresponding coefficient of determination was calculated. The Kruskal-Wallis test was used for group comparisons. Statistical significance was set at  $P < .05$ . The SPSS 12.0 statistical package was used (SPSS Inc. Chicago, Illinois, USA).

#### Results

After discarding patients who met an exclusion criterion ( $n=5$ ) and those whose peptide analysis and echocardiographic study were

performed more than 15 days after blood sampling ( $n=11$ ), 98 patients were finally included in the analysis.

#### Clinical Profile and Echocardiography

Tables 1 and 2 show the clinical profile and echocardiographic characteristics of the series studied. Of the 98 patients, 31 (31.6%) had some sort of left ventricular structural abnormality (increased VST, posterior wall thickness, and/or EDD). Only 1 patient showed decreased left ventricular systolic function, associated with increased EDD in the same ventricle.

#### Correlation Analysis

NT-proBNP concentration was significantly correlated with VST ( $r=0.63$ ), the left ventricular posterior wall thickness ( $r=0.45$ ), and left ventricular EDD ( $r=0.51$ ) ( $P < .0001$  for all correlations). In Figure 1, the linear and squared correlations are plotted along with the coefficient of determination ( $R^2$ ).

**Table 1**

Clinical Profile of the Patients ( $n=98$ )<sup>a</sup>

Mean age, y	54 (13)
Men	72%
Body mass index, kg/m <sup>2</sup>	32 (5)
Hypertension	48%
Confirmed COPD (GOLD stage I)	4%
Months since onset of symptoms <sup>b</sup>	48 (24-60)
Apnea-hypopnea index	40 (18)
Desaturation index >4%	37 (19)
Epworth score	12 (5)
CT90 <sup>b</sup>	11% (3-23)
Mean SaO <sub>2</sub> <sup>b</sup>	93% (92-95)
Minimum SaO <sub>2</sub> <sup>b</sup>	76% (64-81)
Creatinine, mg/dL <sup>b</sup>	1.0 (0.9-1.1)
NT-proBNP, pg/mL <sup>b</sup>	50 (20-91)
FEV <sub>1</sub> , % predicted	97% (31%)
Presenting complaint	
Snoring	43%
Apneas	37%
Daytime sleepiness	19%
Other	1%
Severity of SAHS <sup>10</sup>	
Mild	7%
Moderate	29%
Severe	64%

Abbreviations: COPD, chronic obstructive pulmonary disease; CT90, cumulative percentage of night with SaO<sub>2</sub><90%; GOLD, Global Initiative for Chronic Obstructive Lung Disease; NT-proBNP, N-terminal fragment of brain natriuretic peptide; SAHS, sleep apnea-hypopnea syndrome; SaO<sub>2</sub>, oxygen saturation.

<sup>a</sup>Data are expressed as means (SD) and or medians (interquartile range).

<sup>b</sup>Kolmogorov-Smirnov test for normal distribution with  $P < .05$ .

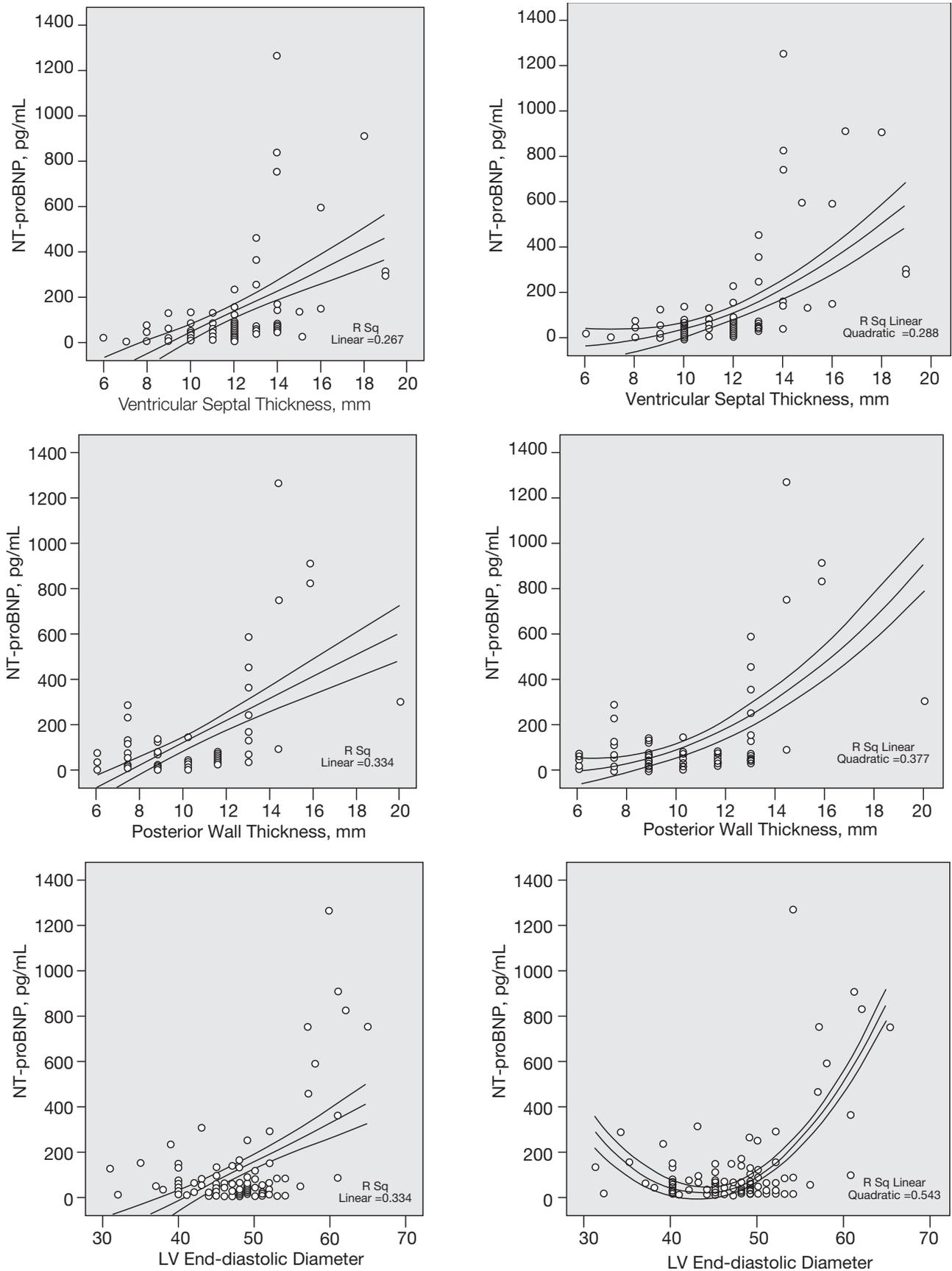
**Table 2**

Echocardiographic Characteristics of the 98 Patients Analyzed

Right ventricular end-diastolic diameter, mm	23.1 (5.3)
Ventricular septal thickness, mm <sup>b</sup>	12 (10-13)
Left ventricular end-diastolic diameter, mm	47.6 (6.3)
Left ventricular end-systolic diameter, mm	27.6 (5.4)
Left ventricular posterior wall thickness, mm <sup>b</sup>	10 (10-12)
Left ventricular diameter, mm	37.5 (6.3)
Decrease in left ventricular function	1 patient
Decrease in right ventricular function	0 patients
Peak mitral E-wave velocity, cm/s	69.6 (19.7)
Peak mitral A-wave velocity, cm/s	75.7 (18.3)
Left ventricular isovolumetric relaxation time, ms <sup>b</sup>	100 (90-110)
Peak tricuspid E-wave velocity, cm/s	54.8 (10.3)
Peak tricuspid A-wave velocity, cm/s	57.4 (15.7)
Right ventricular isovolumetric relaxation time, ms	69.2 (27.7)

<sup>a</sup>Data are expressed as means (SD) and or medians (interquartile range).

<sup>b</sup>Kolmogorov-Smirnov test for normal distribution with  $P < .05$ .



**Figure 1.** Plot of significant correlations ( $P < .0001$ ) of the plasma concentrations of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) against ventricular septal thickness (top plots), posterior wall thickness (middle plots), and left ventricular (LV) end-diastolic diameter (bottom plots). The squared correlation (right plots) provides a better coefficient of determination ( $R^2$ ) than the linear correlation (left plots), particularly for LV end-diastolic diameter.

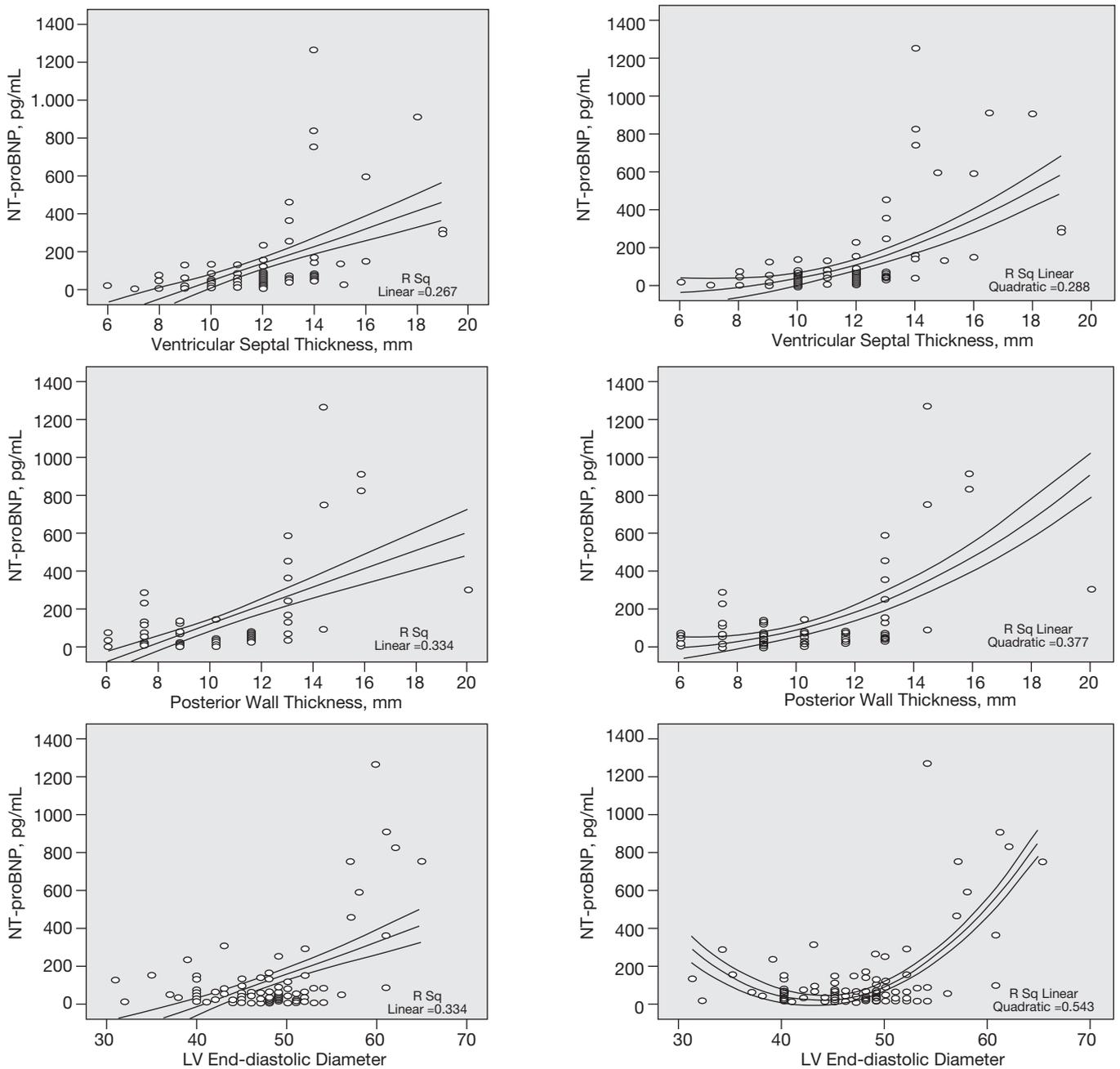


Figure 1. (Continued.)

*NT-proBNP and Severity of Heart Disease*

There were significant differences in NT-proBNP concentrations in patients without cardiac abnormalities and those who had one or more abnormality (increased VST, left ventricular posterior wall thickness, or left ventricular EDD) ( $P < .0001$  for all comparisons), as shown in Figure 2.

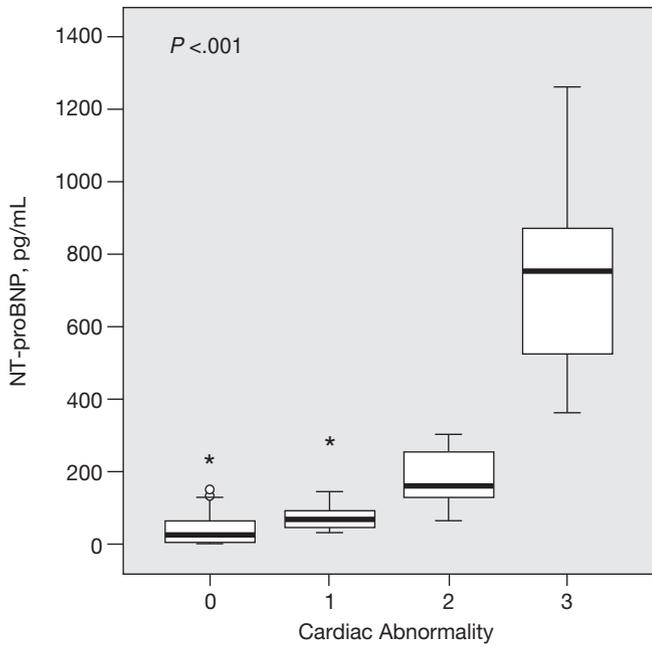
*ROC Curve Analysis*

NT-proBNP concentrations were assessed according to the presence of cardiac abnormalities. The area under the ROC curve was significant ( $P < .0001$ ). Figure 3 shows the sensitivity and specificity for classifying patients with cardiac abnormalities. Assuming that

specificity would be more useful for clinical practice, we calculated that an NT-proBNP concentration of 100 pg/mL yielded a sensitivity of 55%, a specificity of 90%, a positive predictive value of 70%, and a negative predictive value of 80%, while an NT-proBNP concentration of 200 pg/mL yielded a sensitivity of 36%, of specificity of 100%, a positive predictive value of 92%, and a negative predictive value of 77%. Thus, NT-proBNP concentrations less than 100 and 200 pg/mL could rule out structural abnormalities with a reliability of 90% and 100%, respectively.

**Discussion**

SAHS is the most common type of sleep-disordered breathing,<sup>1</sup> affecting 4%-6% of middle-aged men and 2%-4% of middle-aged



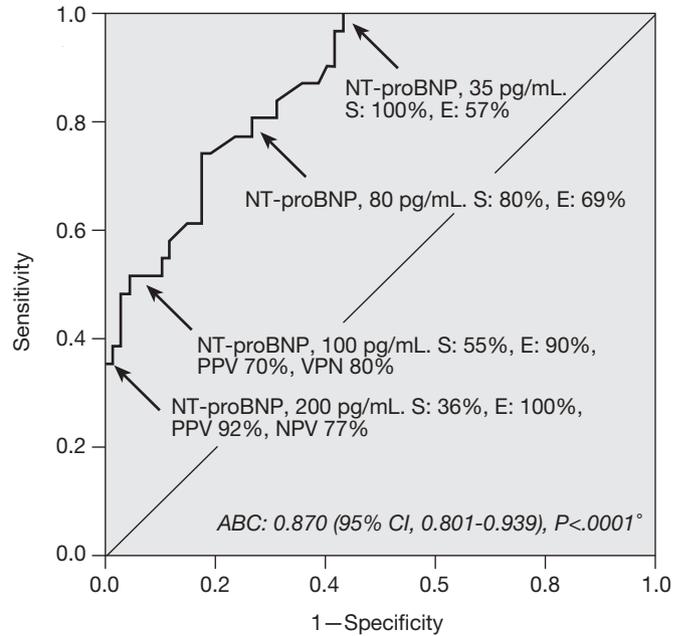
Patients	67	18	5	8
NT-proBNP	29 (10-63)	72 (48-108)	164 (103-281)	757 (493-893)

**Figure 2.** Box plots showing the range of concentrations of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) in patients with sleep apnea-hypopnea syndromes without cardiac abnormalities (0), and with 1, 2, or 3 abnormalities (ventricular septal thickness, posterior wall thickness, or left ventricular end-diastolic diameter) ( $P < .0001$ ). The table below the figure indicates the number of patients in each group and the median (interquartile range). The circles indicate values between 1.5 and 3 times the upper limit of the interquartile range (atypical values), and the asterisks values more than 3 times the upper limit of the interquartile range (extreme values).

women.<sup>2</sup> In addition to the negative impact on the social life of the patient, SAHS is very detrimental to the health of sufferers because it is a strong cardiovascular risk factor.<sup>3,4</sup>

It is thought that SAHS influences the cardiovascular system through the mechanical effect of apneas on intrathoracic pressures, with repercussions on cardiac function, and intermittent hypoxia, which causes overstimulation of the sympathetic system and endothelial cell dysfunction.<sup>5</sup> The Sleep Heart Health Study reported relative odds of 2.38 for heart failure in patients with SAHS compared to those without, a level of risk that was higher than for hypertension, ischemic heart disease, and stroke.<sup>4</sup> Given the prognostic implications of heart failure in patients with SAHS,<sup>11</sup> early diagnosis is necessary. Doppler echocardiography is a simple, inexpensive, noninvasive technique that is widely available. Use of this technique in these patients has permitted the detection of structural abnormalities<sup>12</sup> and systolic and diastolic dysfunction.<sup>13,14</sup> However, it would be impossible to perform echocardiography in all patients with SAHS; if a biological marker were available, this could help select patients for further study.

Brain natriuretic peptide (BNP) is a cardiac neurohormone secreted in the form of proBNP mainly by the ventricles in response to pressure or volume overloads. In the blood stream, this is converted into the active form (BNP) and its inactive NT terminal fraction (NT-proBNP) in a 1 to 1 ratio. Both substances are excellent diagnostic and prognostic markers of heart failure and acute coronary syndrome.<sup>15</sup> Recent studies have shown that NT-proBNP is an important predictor of cardiovascular events in patients with hypertension and left ventricular hypertrophy, particularly when no other cardiovascular comorbidities are present.<sup>16</sup> Therefore,



**Figure 3.** Receiver operating characteristics curve to calculate sensitivity and specificity for concentrations of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) with respect to presence of a cardiac abnormality (ventricular septal thickness, posterior wall thickness, or left ventricular end-diastolic diameter). AUC indicates area under the concentration-time curve; CI, confidence interval; E, specificity; NPV, negative predictive value; PPV, positive predictive value; S, sensitivity.

measurement of concentrations of this marker of myocardial stress in patients with SAHS would help in the early diagnoses of subclinical heart disease that might deteriorate with apneic episodes, and it could also be a useful tool for monitoring such patients.<sup>17</sup>

The patients included in our study had the usual profile in that they were obese men (mean [SD] body mass index, 32 [5] kg/m<sup>2</sup>) who were middle-aged (54 [13] years) and met the criteria for severe SAHS (AHI of 30 in 64%). A clinically relevant left ventricular structural abnormality from the cardiological point of view was present in 31.6% of the cohort (Table 2), even though no patients had signs or symptoms of heart failure. These variables were significantly correlated with plasma concentrations of NT-proBNP. A squared correlation provided a better fit than a linear one (Figure 1); that is, when each variable deviated from normal value, NT-proBNP increased markedly. In addition, a larger number of cardiac abnormalities in a given patient was associated with higher the concentrations of NT-proBNP (Figure 2). The repeated increases in afterload associated with SAHS may be accompanied by compensatory myocardial hypertrophy which, in addition, does not seem to depend on whether hypertension is present,<sup>12,18</sup> as shown by findings for our group.<sup>19</sup> It is therefore not surprising that the NT-proBNP concentration reflects these subclinical abnormalities or that the increases are greater when more abnormalities are present.

Currently, few studies have been published on the role of natriuretic peptides in SAHS, and results have been disparate and focused on acute changes during sleep. In SAHS, BNP concentrations increase with systolic blood pressure and longer durations of apnea, whereas they remain constant in healthy individuals<sup>20</sup> and return to normal in patients who receive effective CPAP therapy. Svatikova et al,<sup>21</sup> who compared levels of different peptides in groups of SAHS sufferers with and without cardiovascular comorbidity and in healthy controls, concluded that SAHS is associated with acute increases in levels of atrial natriuretic peptide during apneic sleep but the situation improves with CPAP, whereas BNP did not vary as would be expected, at least in the group of patients with SAHS and severe heart failure.

Their results contradict many of the studies conducted in patients with heart failure,<sup>22</sup> possibly because they included a small number of patients. In a more recent study with a similar design and methodology to ours, the impact of SAHS on plasma concentrations of NT-proBNP and the effect of CPAP were investigated.<sup>23</sup> The group of patients with SAHS was divided into those with and without hypertension, and compared with a control group. No differences were found in baseline levels of NT-proBNP, although there was a significant decrease after treatment with CPAP in both groups with SAHS. The authors drew attention to the higher levels of the peptide in patients with hypertension, although the differences were not statistically significant. While differences may have been significant if more patients had been studied, group differences in terms of age, number of women, and body mass index—all factors that directly influence plasma concentrations of NT-proBNP<sup>6</sup>—suggest that the results should be interpreted with caution. In any case, the physiology of secretion of these peptides should be borne in mind when using them as markers. Atrial natriuretic peptide is stored in granules in the atria and can be released rapidly. It has a short half-life (2-5 minutes) and is quickly removed from the blood stream. BNP on the other hand is not stored and so a more prolonged stimulus is required for it to be released. Atrial natriuretic peptide is a quick-response hormone, whereas BNP and NT-proBNP are better indicators of chronic cardiac overload and so are recommended as markers of chronic ventricular dysfunction.<sup>6</sup>

In a recent study, Hübner et al<sup>24</sup> found that NT-proBNP concentrations did not correlate with severity of SAHS measured by AHI. Although this finding might seem to contradict or invalidate our findings, it does not. Their multiple regression model, in which data for 28 patients were entered, identified greater left ventricular mass and worse left ventricular ejection fraction to be independent predictors of plasma concentrations of NT-proBNP along with other previously recognized myocardial risk factors such as renal function, age, and hypertension. These data are consistent with our findings: the greater the cardiac repercussion, the larger the increase in NT-proBNP, as these cardiac abnormalities that accompany SAHS would be responsible for elevation of the peptide.

We found 2 cutoff points for NT-proBNP with low sensitivity but very high specificity and negative predictive values, making it the ideal marker for screening for silent heart disease. With NT-proBNP concentrations of 200 pg/mL or higher, it is likely that we will be referring patients to cardiology with at least 1 detectable structural abnormality and the prognostic value is clear.

In this study, we have not analyzed the correlation between diastolic dysfunction and concentrations of NT-proBNP. While diastolic dysfunction is present in a substantial number of these patients,<sup>18</sup> almost 30% of the healthy population with similar morphometric characteristics also show similar dysfunction.<sup>18,25</sup> We therefore believe that asymptomatic structural abnormalities are of great clinical significance and prognostic value when selecting patients for referral to cardiology.

From our point of view, this study has important implications for the management of patients with SAHS. Detection of subclinical heart disease by readily reproducible and minimally invasive methods, such as the measurement of plasma NT-proBNP concentration, will help select patients for referral to cardiology without overloading echocardiography units. It can be expected that early diagnosis has a favorable impact on morbidity and mortality in SAHS.

The chief limitation of our study is the fact that we mainly used respiratory polygraphy as the diagnostic method for SAHS. This technique is very widely used, however, and its use is sufficiently well supported by consensus statements<sup>8</sup> and international guidelines.<sup>26</sup> In view of the long waiting lists for polysomnography, respiratory polygraphy has become the most widely used diagnostic method and even the one that is most used to adjust CPAP devices.<sup>27</sup> A second limitation might be not having divided the patients into

2 groups with and without hypertension, as done by other authors,<sup>23</sup> but our own data,<sup>19</sup> consistent with previous studies,<sup>12</sup> suggest that this step would be unnecessary. A third limitation might be the fact that conventional transthoracic echocardiography was used instead of more accurate techniques such as tissue Doppler imaging,<sup>28</sup> but the equipment necessary is not available to all echocardiography units at present. The aim of our study was to mirror the current situation of respiratory medicine specialists in sleep clinics whose patients with SAHS may be candidates for referral to cardiology, and conventional transthoracic echocardiography remains the most widely available and widely used diagnostic method. We therefore think that these limitations do not detract from the importance of our results.

In summary, a substantial proportion of patients with SAHS had asymptomatic cardiac structural abnormalities that were positively correlated with plasma concentrations of NT-proBNP. This measure may serve as a marker of silent heart disease, identifying candidates for referral to cardiology.

## References

1. Redline S. Epidemiology of sleep-disordered breathing. *Semin Respir Crit Care Med.* 1998;19:113-22.
2. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med.* 1993;328:1230-5.
3. McNicholas WT, Bonsignore MR and the Management Committee of EU COST ACTION B26. *Eur Respir J.* 2007;29:156-78.
4. Shahar E, Whitney CW, Redline S, Lee ET, Newman AB, Nieto FJ, et al. Sleep-disordered breathing and cardiovascular disease: cross-sectional results of the Sleep Heart Health Study. *Am J Respir Crit Care Med.* 2001;163:19-25.
5. Dincer HE, O'Neill W. Deleterious effects of sleep-disordered breathing on the heart and vascular system. *Respiration.* 2006;73:124-30.
6. Almenar Bonet, L, Martínez-Dolz L. Péptidos natriuréticos en insuficiencia cardíaca. *Rev Esp Cardiol.* 2006;6 Supl:15F-26F.
7. Dingli K, Coleman EL, Vennelle M, Finch SP, Wraith PK, McKay TW, et al. Evaluation of a portable device for diagnosing the sleep apnoea/hypopnoea syndrome. *Eur Respir J.* 2003;21:253-9.
8. Consenso Español sobre el síndrome de apneas-hipopneas del sueño (SAHS). Grupo Español de Sueño. *Arch Bronconeumol.* 2005;41:51-67.
9. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the Joint National Committee in Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Hypertension.* 2003;42:1206-52.
10. Global Initiative for Chronic Obstructive Lung Disease. Update 2007. Available from: <http://www.goldcopd.com>
11. Lavie P, Herer P, Lavie L. Mortality risk factors in sleep apnoea: a matched case-control study. *J Sleep Res.* 2007;16:128-34.
12. Hedner J, Ejnell H, Caidahl K. Left ventricular hypertrophy independent of hypertension in patients with obstructive sleep apnoea. *J Hypertens.* 1990;8:941-6.
13. Laaban JP, Pascal-Sebaouns S, Bloch E, Orvoen-Frija E, Oppert JM, Huchon G. Left ventricular systolic dysfunction in patients with obstructive sleep apnoea syndrome. *Chest.* 2002;122:1133-8.
14. Fung JW, Li TS, Choy DK, Yip W, Ko FW, Sandersen JE, et al. Severe obstructive sleep apnea is associated with left ventricular diastolic dysfunction. *Chest.* 2002;121:422-9.
15. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatine MS, McCabe CH, et al. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med.* 2001;345:1014-21.
16. Olsen MH, Wachtell K, Tuxen C, Fossum E, Bang LE, Hall C, et al. N-terminal pro-brain natriuretic peptide predicts cardiovascular events in patients with hypertension and left ventricular hypertrophy: a LIFE study. *J Hypertens.* 2004;22:1597-604.
17. Vartany E, Imevbore M, O'Malley M, Manfredi C, Pasquarella C, Scinto L, et al. N-terminal pro-brain natriuretic peptide for detection of cardiovascular stress in patients with obstructive sleep apnoea syndrome. *J Sleep Res.* 2006;15:424-9.
18. Moro JA, Almenar L, Fernández-Fabrellas E, Ponce S, Blanquer R, Salvador A. Alteraciones ecocardiográficas asociadas al síndrome de apnea-hipopnea del sueño en función de su gravedad. *Rev Esp Cardiol.* 2007;60:589-96.
19. Moro JA, Almenar L, Fernández-Fabrellas E, Ponce S, Blanquer R, Salvador A. Análisis de las alteraciones ecocardiográficas del síndrome de apnea e hipopnea del sueño y su modificación con la presencia de hipertensión arterial. *Rev Esp Cardiol.* 2008;61:49-57.
20. Kita H, Ohi M, Chin K, Noguchi T, Otsuka N, Tsuboi T, et al. The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnoea and its response to therapy with nasal continuous positive airway pressure. *J Sleep Res.* 1998;7:199-207.
21. Svatikova A, Shamsuzzaman AS, Wolk R, Phillips BG, Olson LJ, Somers VK. Plasma brain natriuretic peptide in obstructive sleep apnea. *Am J Cardiol.* 2004;94:529-32.
22. Lubien E, deMaria A, Krishnaswamy P, Copton P, Koon J, Kazanegra R, et al. Utility of B-natriuretic peptide in detecting diastolic dysfunction: comparison with Doppler velocity recordings. *Circulation.* 2002;105:595-601.

23. Tasci S, Manka R, Scholtyssek S, Lentini S, Troatz C, Stoffel-Wagner B, et al. NT-proBNP in obstructive sleep apnea syndrome is decreased by nasal continuous positive airway pressure. *Clin Res Cardiol.* 2006;95:23-30.
24. Hübner R-H, El Mokhtari NE, Freitag S, Rausche T, Göder R, Tiroke A, et al. NT-proBNP is not elevated in patients with obstructive sleep apnea. *Respir Med.* 2008;102:134-42.
25. Fischer M, Baessler A, Hense HW, Hengsternberg C, Muscholl M, Holmer S, et al. Prevalence of left ventricular diastolic dysfunction in the community. Results from a Doppler echocardiographic-based survey of a population sample. *Eur Heart J.* 2003;24:320-8.
26. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D, Coleman J Jr, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. *Sleep.* 2005;28:499-521.
27. Mulgrew AT, Fox N, Ayas NY, Ryan F. Diagnosis and initial management of obstructive sleep apnea without polysomnography. A randomized validation study. *Ann Intern Med.* 2007;146:157-66.
28. Shivalkar B, van de Heyning C, Kerremans M, Rinkevich D, Verbraecken J, de Backer W, et al. Obstructive sleep apnea syndrome: more insights on structural and functional cardiac alterations, and the effects of treatment with continuous positive airway pressure. *J Am Coll Cardiol.* 2006;47:1433-9.