

## NT-proBNP and Atrioventricular Plane Displacement. Relationship and Diagnostic Implications

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**Introduction and objectives.** NT-proBNP is useful in the diagnosis of heart failure and ventricular dysfunction. Left atrioventricular plane displacement (AVPD) is a consolidated index of ventricular function. Our objective was to carry out a multicenter population-based study to establish the relationship between plasma NT-proBNP levels with AVPD values.

**Patients and method.** We studied 215 subjects (age  $66 \pm 9$  years; 57.7% women) chosen from a random sample of 432 people from the Community of Valencia, who previously reported suffering from some degree of dyspnea. Doppler echocardiography was done, AVPD was calculated and plasma NT-proBNP concentrations were determined. All studies were completed in 194 patients.

**Results.** For the whole population NT-proBNP was  $88 (0-2,586)$  pg/ml and AVPD was  $11.9 \pm 1.6$  mm. NT-proBNP concentration correlated well with AVPD ( $r = 0.44$ ;  $p < 0.00001$ ), and higher peptide levels were obtained in AVPD quartiles that indicated less displacement ( $p < 0.05$ ). When NT-proBNP values were grouped according to their association with AVPD lower or higher than the 50th percentile AVPD, the difference was significant at  $p < 0.01$ . When AVPD values lower and higher than 10 mm were compared, NT-proBNP values were higher in persons with AVPD lower than 10 mm ( $p < 0.05$ ).

**Conclusions.** This population study found higher NT-proBNP concentrations in subjects with lower AVPD, and illustrates the potential diagnostic usefulness of NT-proBNP in clinical practice.

**Key words:** *Natriuretic peptides. Echocardiography. Heart failure.*

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### NT-proBNP y desplazamiento del plano auriculoventricular. Relación e implicaciones diagnósticas

**Introducción y objetivos.** El N-terminal propéptido natriurético cerebral (NT-proBNP) es útil en el diagnóstico de la insuficiencia cardíaca y la disfunción ventricular. El desplazamiento del plano auriculoventricular (DPAV) es un índice consolidado de la función ventricular. Nuestro objetivo es relacionar en un estudio multicéntrico poblacional los valores plasmáticos del NT-proBNP y los valores del DPAV.

**Pacientes y método.** Estudiamos a 215 sujetos (edad,  $66 \pm 9$  años; un 57,7%, mujeres) obtenidos de una muestra aleatoria de 432 personas de la Comunidad Valenciana que previamente declararon sufrir algún grado de disnea. Se realizó un estudio con eco-Doppler, se midió el DPAV y se determinó el valor plasmático de NT-proBNP. El estudio se completó en 194 pacientes.

**Resultados.** Para toda la población, el valor de NT-proBNP fue de 88 pg/ml (rango, 0-2.586 pg/ml) y el valor del DPAV fue de  $11,9 \pm 1,6$  mm. Las concentraciones del péptido natriurético muestran una correlación con los valores del DPAV ( $r = 0,44$ ;  $p < 0,00001$ ) y su valores más elevados se observan en los cuartiles del DPAV con menor desplazamiento ( $p < 0,05$ ). Cuando agrupamos los valores del NT-proBNP en menor o mayor del percentil 50 del DPAV, obtuvimos un valor de  $p < 0,01$ . Si dividimos el DPAV en mayor o menor de 10 mm, los valores de NT-proBNP son más elevados en los sujetos con DPAV menor de 10 mm ( $p < 0,05$ ).

**Conclusiones.** Este estudio poblacional muestra valores más altos de NT-proBNP en sujetos con un desplazamiento menor del plano auriculoventricular, y pone de manifiesto su potencial diagnóstico en la práctica clínica.

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

## INTRODUCTION

Heart failure is a major health problem in developed countries because of associated morbidity and

## ABBREVIATIONS

AVPD: atrioventricular plane displacement.  
EF: ejection fraction.  
NT-proBNP: N-terminal pro-brain natriuretic peptide.  
PANES: prevalence of angina in Spain.  
Vp: mitral valve flow propagation velocity.

mortality. The already high prevalence and incidence of heart failure continue to increase<sup>1</sup> because of general living conditions (higher mean age of the population) and the appearance of new drugs and health technologies that prolong post-infarction survival.

The importance of neurohormonal systems involved in the physiopathology of heart failure has been known for some time.<sup>2-5</sup> Noteworthy among these systems, because of its importance for diagnosis and prognosis, is the family of natriuretic peptides.<sup>6</sup> To date three natriuretic peptides have been reported: atrial, brain and type C. The first two are used as markers in the diagnosis, prognosis and treatment of cardiovascular disease.<sup>7-9</sup> Atrial and brain natriuretic peptides are synthesized by cardiomyocytes as prohormones, encoded by different genes,<sup>10</sup> whereas type C is synthesized by endothelial cells.

From a biochemical point of view, atrial natriuretic peptide is released from the atrium as a prohormone, and is cleaved into amino-terminal and carboxy-terminal fragments that correspond to the biologically active hormone. Brain natriuretic peptide was discovered initially in porcine brain,<sup>11</sup> and was later found in the human brain, then in larger amounts in the heart ventricles.<sup>10</sup> It is synthesized as a prohormone, then cleaved by a protease to yield an amino-terminal fragment (NT-proBNP) and a mature peptide molecule that corresponds to the biologically active hormone. Both peptides possess a wide spectrum of functions that includes stimulation of natriuresis, vasodilation, and inhibition of the renin-angiotensin-aldosterone system and activity of the sympathetic nervous system.<sup>12</sup> The exact mechanism of release is under study, but it is known that the concentrations of these peptides are related to increased heart wall stress and are elevated in patients with ventricular hypertrophy and systolic or diastolic ventricular dysfunction.<sup>13</sup> This characteristic makes these peptides useful as biochemical markers of heart failure.<sup>14-16</sup> In addition, plasma concentrations have been related to ejection fraction, degree of ventricular dysfunction, and other hemodynamic parameters.<sup>17,18</sup>

Atrioventricular plane displacement (AVPD) measures longitudinal function of the left ventricle and is a well-known and valuable indicator of systolic and diastolic ventricular function.<sup>19-21</sup> This measure is particularly useful in patients who require quantification of ventricular function but who have a poor acoustic window that makes it difficult to detect the endocardial borders despite the enhancements provided by the use of contrast media<sup>22,23</sup> and new technologies for border visualization.<sup>24,25</sup>

In this multicenter, population-based study we searched for relationships between AVPD values and plasma concentrations of NT-proBNP in a population of individuals with dyspnea. Our aim was to determine to what degree these values reflected variations in plane displacement.

## PATIENTS AND METHODS

### Patients

Our sample of subjects was drawn from the PANES (Prevalence of Angina in Spain) database, and patients residing in the Community of Valencia who reported suffering from dyspnea were selected. The PANES study methods have been described elsewhere.<sup>26</sup> Basically, this was a cross-sectional study carried out during 1995 and 1996 in which a sample of 10 248 inhabitants from the 17 different autonomous communities in Spain were selected as representative of the entire population, and asked to take part in a survey. A two-step sampling procedure was used. First 200 cities stratified by autonomous community were chosen randomly, then three socioeconomic environments were chosen in each city for random sampling. The sampling unit was the household, which included all eligible persons in each family unit. Persons who declined to participate were replaced with members of other family units.

In all, 999 inhabitants from the PANES database were from the Community of Valencia. Of these 432 individuals responded affirmatively to the item that asked whether they had any degree of dyspnea. These 432 participants were then given an appointment at their reference hospital during the year 2000 (10 hospitals participated in the study). At this appointment a blood sample was obtained, Doppler echocardiographic studies were done, and each participant completed a specially-designed questionnaire. Atrioventricular plane displacement was calculated in millimeters. Of these 432 participants, 215 agreed to participate in the present study, 21 had died, 6 were disabled because of severe illness, 131 could not be located and 59 who had agreed to participate did not attend the appointment. All studies could be completed for 194 patients, whose clinical characteristics are summarized in Table 1.

**TABLE 1. Clinical characteristics of the patients**

Total (n=194)	
Sex	
Women	112 (57.7%)
Age, years	66±9
Systolic blood pressure, mm Hg	141±23
Heart rate	73±13
NYHA grade	
I	88 (45.4%)
II	83 (42.7%)
III	23 (11.9%)
Echocardiographic parameters	
EF	64±8
E/A	0.9±0.2
Vp, cm/s	60±19
AVPD, mm	11.9±1.6
Body mass index, g/m <sup>2</sup>	112±47
Creatinine, mg/dL	1.0±0.6
NT-proBNP, pg/mL	88 (0-2.586)

All values are expressed as the mean±SD; NT-proBNP values are expressed as the median (range).

A indicates peak late mitral valve inflow velocity; AVPD, atrioventricular plane displacement; E, peak early mitral valve inflow velocity; EF, ejection fraction; NYHA, New York Heart Association functional grade; Vp, mitral valve flow propagation velocity.

The main cardiologic diagnoses were ischemic heart disease (n=31; 16.0%), significant valve disease (n=7; 3.6%), dilated cardiomyopathy (n=3; 1.5%) and congenital heart disease (n=1; 0.5%). Importantly this study was based on a sample of patients who reported having dyspnea, and no patients without dyspnea were included. Of the 194 patients, 69 (35.6%) were diagnosed as having hypertension. All patients were classified according to the New York Heart Association system as class I (88 persons; 45.4%), class II (83 persons; 42.7%) or class III (23 persons; 11.9%). The sex distribution was 112 women versus 82 men, and mean age was 66 ± 9 years. Other noncardiologic diagnoses were diabetes mellitus (n=30; 15.5%) and lung disease (n=29; 14.9%). Of the 194 subjects in the final sample, 72 (37.1%) were obese (body mass index >30 kg/m<sup>2</sup>).

### Echocardiographic studies

All echocardiographic studies were done with 2.5-MHz transducers and different standard systems habitually used at the 10 participating hospitals. Images and Doppler traces were video-recorded for later analysis by investigators who were blind to the results of other tests. Parasternal and apical planes were obtained with the patient in left lateral decubitus, and measurements were obtained after deep exhalation.

Atrioventricular plane displacement was measured in M mode from two-dimensional 2-chamber and 4-chamber apical projections with a previously

described technique.<sup>20</sup> The AVPD region was the distance covered by the atrioventricular plane between its furthest position from the apex (start of contraction) to its closest approach to the apex (end of contraction including post-ejection shortening). The AVPD was recorded in septal, lateral, posterior and anterior regions. Mean AVPD was calculated for all four regions.<sup>21</sup>

Mitral valve flow propagation velocity (Vp) was measured with the method described by García et al.<sup>27</sup> The A and E waves in the spectrum of mitral valve velocities were measured with pulsed Doppler images at the leaflet tips, and the E/A ratio was calculated. Ejection fraction (EF) was calculated with the area-length method<sup>28</sup> as:

$$\frac{100 \text{ end-diastolic volume} - \text{end-systolic volume}}{\text{end-diastolic volume}}$$

All two-dimensional images, Doppler spectra and color Doppler images were analyzed with a computerized system (Eco-Dat; Software de Medicina, S.A.), and all values were calculated as the mean for 4 heart cycles in sinus rhythm and 8 heart cycles in atrial fibrillation.

### Reproducibility

Interobserver and intraobserver variability were evaluated in series of 50 consecutive patients by 2 observers who examined the same patient consecutively. Variability was expressed as the absolute difference divided by the mean value of the measurements.

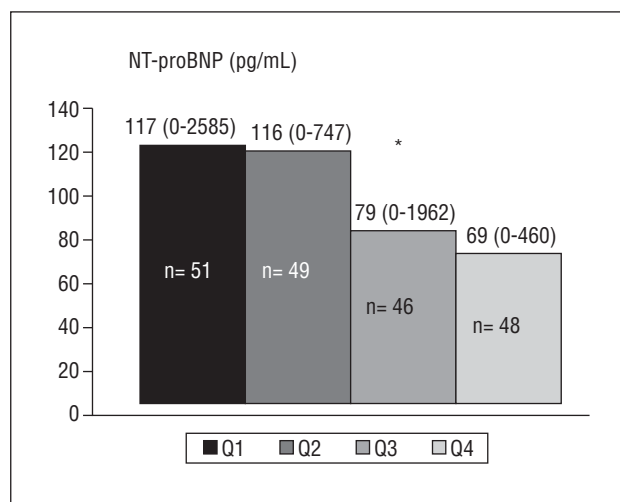
For AVPD determinations, interobserver variability was 4.6±4.9% (range of the differences in AVPD, 0-2 mm), with a mean displacement of 13 mm (range, 10-16 mm). Intraobserver variability was 2.9±4.2% (range of the differences in AVPD, 0-2 mm).

Inter- and intraobserver variability for Vp was 8.0±8.0% and 7.2±8.0%, respectively.

### NT-proBNP analysis

Blood samples were obtained by venipuncture after the participant had remained in the supine decubitus for 30 minutes. Samples were centrifuged at 3000 rpm for 10 minutes at room temperature, then frozen before transportation to the laboratory for blind analysis. The laboratory work was coordinated by the Hospital La Fe in Valencia, where all NT-proBNP measurements were done.

The concentration of NT-proBNP in EDTA-plasma was measured in duplicate by enzyme-linked immunoanalysis *in vitro* (ELISA Kit, Roche Diagnostics). A four-parameter function was used to calculate NT-proBNP values, and concentration was expressed in pg/mL.



**Fig. 1.** Plasma concentration of NT-proBNP in each group according to quartile of AVPD.

\* $P < .05$ .

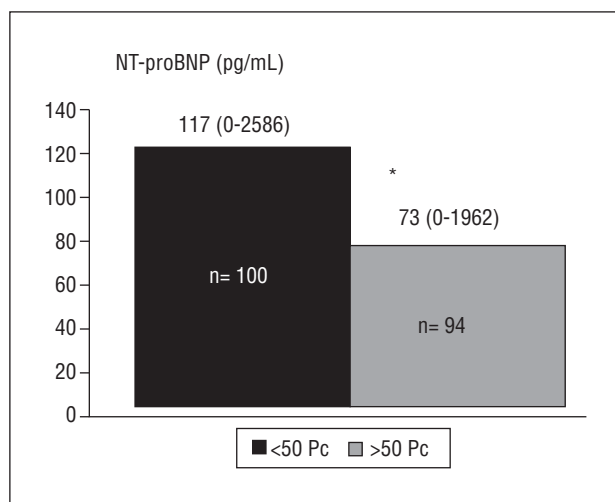
AVPD indicates atrioventricular plane displacement; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartile.

The range of the technique was 0-2.069 pg/mL. Samples with an NT-proBNP concentration above the upper limit were diluted to one-fourth in 0.9% sodium chloride solution, and the results were multiplied by the dilution factor. No cross-reactions were detected with brain, atrial or type C peptides ( $<0.001\%$ ). Inter- and intra-assay and within-assay coefficients of variability in human plasma were within the 1.3%-4.8% range.

## Statistical analysis

Data for quantitative variables were expressed as the mean  $\pm$  standard deviation (SD), except for NT-proBNP, which was expressed as the median and range.

Correlations between NT-proBNP values and plane displacement were sought by calculating correlation coefficients with linear regression and quadratic regression models. A nonparametric test for independent samples was used (Mann-Whitney's U test) to compare NT-proBNP values for participants in the 2 AVPD groups. Analysis of variance (ANOVA) with the Kruskal-Wallis test was used to compare NT-proBNP values between participants in the 4 quartiles of AVPD (Q1=to the 25th percentile; Q2=between the 25th and the 50th percentile; Q3=between the 50th and 75th percentile; Q4=above the 75th percentile). To compare the results of echocardiographic studies in the four AVPD percentile groups we used ANOVA for multiple comparisons. Values of  $P < .05$  were considered statistically significant. All analyses were done with version 10.1 of the SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, Illinois).



**Fig. 2.** Plasma concentration of NT-proBNP in the upper and lower 50th percentile of AVPD.

\* $P < .01$ .

AVPD indicates atrioventricular plane displacement; NT-proBNP, N-terminal pro-brain natriuretic peptide; Pc, percentile.

## RESULTS

For the entire population mean AVPD was  $11.9 \pm 1.6$  mm and median plasma concentration of NT-proBNP was 88 pg/mL (range, 0-2585 pg/mL).

Linear regression analysis showed a correlation between NT-proBNP and AVPD of  $r=0.34$ ;  $y=1025-70.4X$ ;  $P < .00001$ . Quadratic regression analysis showed a correlation of  $r=0.44$ ,  $y=15.2X^2-433X+3.151$ ;  $P < .00001$ .

Quartile values of AVPD (Q1= $10 \pm 1.2$  mm; Q2= $11.6 \pm 0.3$  mm; Q3= $12.45 \pm 0.2$  mm; Q4= $13.9 \pm 1.2$  mm) were contrasted with NT-proBNP, and the following results were obtained for each quartile: Q1, n=51; NT-proBNP 117 pg/mL (range, 0-2585); Q2, n=49; NT-proBNP 116 pg/mL (range, 0-747); Q3, n=46; NT-proBNP 79 pg/mL (range, 0-1962); Q4, n=48; NT-proBNP 69 pg/mL (range, 0-460) ( $P < .05$  in all cases) (Figure 1).

Participants were grouped into the upper (n=94;  $13.2 \pm 1.1$  mm) and lower 50th percentiles for AVPD (n=100;  $10.8 \pm 1.1$  mm), and NT-proBNP concentrations were compared in these 2 groups. The difference between groups was significant at  $P < .01$ . In the upper 50th percentile, the findings were n=94, NT-proBNP 73 pg/mL (range, 0-1962), and in the lower 50th percentile the figures were n=100; NT-proBNP 117 pg/mL (range, 0-2586) (Figure 2).

When we compared NT-proBNP values in participants with AVPD less than and greater than 10 mm, we found a significant difference ( $P < .05$ ) between groups. In group 1, with AVPD  $<10$  mm (n=18), NT-proBNP was 176 pg/mL (range, 7-2586), and in group 2, with AVPD  $>10$  mm



(n=176), NT-proBNP was 85 pg/mL (range, 0-1962) (Figure 3).

When we compared the results for echocardiographic parameters in each quartile of AVPD, we found that for EF and Vp, the differences were significant at  $P<.01$ , whereas for E/A ratio the difference was not significant (Table 2).

## DISCUSSION

Earlier studies have confirmed the close relationship between NT-proBNP concentration and a number of parameters linked to the course of heart failure (New York Heart Association functional class), and with echocardiographic parameters linked to systolic (EF) and diastolic ventricular dysfunction (E/A and Vp).<sup>17,18</sup> These relationships make NT-proBNP a good biochemical marker for the diagnosis, prognosis and treatment of cardiovascular disease.<sup>14-16</sup> Atrioventricular plane displacement has also been shown to be a useful indicator of systolic and diastolic ventricular function, as it correlates well with EF and parameters of diastolic function.<sup>21</sup>

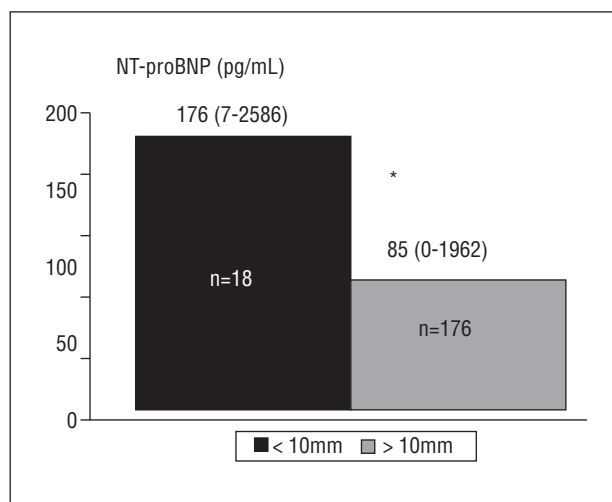
Some patients in whom quantification of ventricular function is necessary have a poor acoustic window, which makes it difficult to visualize the myocardial borders. As a result it is difficult to calculate EF and therefore to evaluate systolic ventricular function. In our study AVPD measurement was a useful approach that can potentially replace EF as the parameter of choice for ventricular function. This is supported by our comparisons of EF values and quartiles of AVPD values ( $P<.01$ ): as EF increased, plane displacement improved (Table 2). We also found a significant difference  $P<.01$  for Vp values in each quartile of AVPD.

We found a significant correlation between NT-proBNP concentration and the magnitude of AVPD ( $r=0.34$ ;  $P<.00001$ ), and this correlation was even stronger in the quadratic regression analysis ( $r=0.44$ ;  $P<.00001$ ).

When we compared NT-proBNP values for different percentile groups of AVPD we found significant differences between quartiles ( $P<.05$ ). The highest concentrations of the peptide were found in association with the smallest plane displacements (Figure 1). This finding is consistent with the mechanism of peptide release during myocardial fiber lengthening.<sup>14</sup>

The difference between groups persisted when AVPD values were grouped into 50th percentiles, with  $P<.01$ . The cut-off value of 10 mm (Figure 2). was used because earlier studies reported displacements of 10 mm or greater as normal.<sup>29</sup>

Our results document the relationship between NT-proBNP values and the magnitude of AVPD. Elevated



**Fig. 3.** Plasma concentration of NT-proBNP in patients with AVPD above and below the cut-off value of 10 mm.

\* $P<.05$ .

AVPD indicates atrioventricular plane displacement; NT-proBNP, N-terminal pro-brain natriuretic peptide.

concentrations of this peptide are seen in connection with diminished plane displacement, a relationship that lends support to the usefulness of NT-proBNP as a biochemical marker of heart failure in the general population. This molecule is also useful to determine the degree of ventricular dysfunction in patients with a poor acoustic window.<sup>30</sup>

## Limitations of the study

To measure plasma NT-proBNP concentration, we used a first-generation Roche Diagnostics ELISA; this may account for the large range of values (from 0 to 2586 pg/mL) and for the modest limit of detection. However, this did not interfere with the consistency between NP-proBNP concentrations and echocardiographic findings (Table 2).

**TABLE 2. Comparison of electrocardiographic variables for patients in each of the four quartiles of AVPD**

Variables	AVPD				P
	Q1 (10±1.2) (n=51)	Q2 (11.6±0.3) (n=49)	Q3 (12.5±0.2) (n=46)	Q4 (13.9±1.2) (n=48)	
EF	56±9	63±6	67±4	69±4	**
Vp	54±20	57±19	63±19	66±17	**
E/A	0.8±0.3	0.85±0.2	0.9±0.2	0.9±0.2	NS

All values are expressed as the mean±SD.

A indicates peak late mitral valve inflow velocity; AVPD, atrioventricular plane displacement; E, peak early mitral valve inflow velocity; EF, ejection fraction; NS, not significant; Q, quartile; Vp, mitral valve flow propagation velocity.

\*\* $P<.01$ .

Earlier studies reported that NT-proBNP values were elevated in patients with mitral and aortic valve regurgitation.<sup>31,32</sup> This would explain the occasional finding, in our participants, of AVPD values within the normal range despite the elevated NT-proBNP concentration in patients diagnosed as having valve disease with good ventricular function.

The use of different Doppler echocardiography scanners may have introduced variability in image acquisition. However, all members of the study group were experienced in using these echocardiography devices at the participating center. To help ensure uniformity in image acquisition procedures, a videotaped demonstration of the procedure was sent to each participating hospital.

## CONCLUSIONS

The data from the present study support the role of NT-proBNP as a biochemical marker of ventricular function in patients with a poor acoustic window. The relationship between this marker and AVPD was also found to be of use. Follow-up studies in patients with heart failure will establish the role of this marker in clinical and therapeutic decision-making.

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