CHEST®

Official publication of the American College of Chest Physicians

Biomarkers of Heart Failure in Pleural Fluid

José M. Porcel, Montserrat Martínez-Alonso, Gonzalo Cao, Silvia Bielsa, Ana Sopena and Aureli Esquerda

Chest 2009;136;671-677; Prepublished online April 10, 2009;
DOI 10.1378/chest.09-0270

CHEST

Original Research

PLEURAL EFFUSION

Biomarkers of Heart Failure in Pleural Fluid

José M. Porcel, MD, FCCP; Montserrat Martínez-Alonso, BSc Stats; Gonzalo Cao, PharmD; Silvia Bielsa, MD; Ana Sopena, PharmD; and Aureli Esquerda, PharmD

Background: **The objective of this study was to compare the diagnostic accuracy of pleural fluid brain natriuretic peptide (BNP), N-terminal pro-BNP (NT-pro-BNP) and ST2, which are biomarkers of myocyte stress, for diagnosing pleural effusions due to heart failure (HF). BNP and ST2 have not been previously evaluated in pleural fluid.**

Methods: **The three biomarkers were measured in the pleural fluid of 90 cardiac effusions and 91 noncardiac effusions by commercially available methodologies. The area under the curve (AUC) quantified the overall diagnostic accuracy of the tests.**

Results: **Pleural fluid NT-pro-BNP, BNP, and ST2 demonstrated AUCs of 0.96, 0.90 and 0.59, respectively, for diagnosing effusions due to HF. The cutoff values of 1,300 and 115 pg/mL, respectively, for NT-pro-BNP and BNP had the best discriminating properties. The reference level for BNP was particularly accurate in men > 75 years of age (AUC, 0.98), but age, gender, and serum creatinine level did not influence the NT-pro-BNP levels. Of the 20 patients whose cardiac effusions were misclassified as exudates by the criteria of Light et al, 18 patients (90%) and 14 patients (70%), respectively, would have been correctly categorized by NT-pro-BNP and BNP, whereas only 10 patients (50%) would have been appropriately classified by the serum-pleural protein gradient.**

Conclusions: **The pleural fluid NT-pro-BNP level is very useful in establishing the diagnosis of HF-associated effusions, and it confirms this diagnosis better than pleural BNP levels. The measurement of NT-pro-BNP rather than the serum-to-pleural protein gradient is recommended for identifying mislabeled cardiac transudates. The pleural fluid ST2 level is not helpful in diagnosing HF.**

(CHEST 2009; 136:671–677)

Abbreviations: AUC = area under the curve; BNP = brain natriuretic peptide; CI = confidence interval; ECLIA = electrochemiluminescence; HF = heart failure; IL = interleukin; IQR = interquartile range; LR = likelihood ratio; NT-pro-BNP = N-terminal pro-brain natriuretic peptide; ROC = receiver operating characteristic

There is overwhelming evidence that the use of natriuretic peptide levels, either brain natriuretic peptide (BNP) or the amino-terminal fragment N-terminal pro-BNP (NT-pro-BNP), provides clinically important information for the diagnosis, prognosis, and management of heart failure (HF).[1] These neurohormones are predominantly secreted from the left and the right cardiac ventricle in response to volume and pressure overload. BNP derives from the precursor pre-pro-BNP, which contains 134 amino acids and includes a signal peptide of 26 amino acids. Pro-BNP, produced by cleavage of the signal pep-

For editorial comment see page 656

Manuscript received February 2, 2009; revision accepted March 4, 2009.

Affiliations: From the Departments of Internal Medicine (Drs. Porcel and Bielsa), Medical Biostatistics (Ms. Martínez-Alonso), and Laboratory Medicine (Drs. Cao, Sopena, and Esquerda), Pleural Diseases Unit, Arnau de Vilanova University Hospital, Institut de Recerca Biomèdica de Lleida, Lleida, Spain.

Funding/Support: Dr. Bielsa is supported by a grant from the Fondo de Investigación Sanitaria (FIS CM07/00020), Instituto de Salud Carlos III, Madrid, Spain.

Correspondence to: José M. Porcel, MD, FCCP, Department of Internal Medicine, Arnau de Vilanova University Hospital, Avda Alcalde Rovira Roure 80, 25198 Lleida, Spain; e-mail: jporcelp@yahoo.es

DOI: 10.1378/chest.09-0270

tide, is further split into BNP (32 amino acids), which is the biologically active hormone, and an inactive NT-pro-BNP (76 amino acids).[2]

Several studies[3] have demonstrated that NT-pro-BNP levels are elevated in the pleural fluid and serum of patients who have HF and a pleural effusion, and this test has been noted to be very accurate for discriminating cardiac effusions from noncardiac effusions. However, BNP, which is measured in many hospital laboratories, has not been evaluated in pleural fluid for its accuracy in diagnosing effusions due to HF.

ST2 is an interleukin (IL)-1 receptor family member whose ligand appears to be IL-33.[4] The ST2/IL-33 signaling is thought to play an important role in the myocardial response to biomechanical overload in stretched myocytes, in a manner similar to natriuretic peptides. The serum levels of the soluble ST2 protein have been found to correlate with the severity of HF.[5] Nevertheless, no information is currently available on the diagnostic value of pleural fluid concentrations of ST2.

Our goal was to investigate whether pleural fluid NT-pro-BNP, BNP, and ST2 have similar operating characteristics for the diagnosis of HF in patients presenting with pleural effusion. We hypothesized that BNP and NT-pro-BNP would have strong correlation and, therefore, nearly identical performances for identifying cardiac effusions. Additionally, we put forward the hypothesis that soluble ST2 levels might be increased in the pleural fluid of patients with HF.

Materials and Methods

We performed a retrospective analysis of patients with pleural effusion from a prospectively maintained database. To do so, we selected 86 consecutive patients from a previous prospective study[6] (50 patients with HF and 36 patients with noncardiac effusions), adding 95 newer patients (40 patients with HF and 55 patients with noncardiac effusions) who had been entered into our computerized database from the periods 2001 to 2004 and 2007 to 2008. In this latter group, the selected patients with HF were consecutive, whereas we performed a stratified choice of noncardiac effusions in order to ensure a proportionate number of patients among the different etiologies, and a comparable sample size between cardiac and noncardiac groups as well. We recorded demographic, clinical, and analytical (pleural fluid and serum) information from all patients who comprised the study population. During the initial evaluations, a 5-mL sample of pleural fluid was collected in a separate tube containing ethylenediaminetetraacetic acid, which was centrifuged at 4°C; subsequently, the supernatant was frozen at −80°C until the natriuretic peptide and ST2 assays were performed. Our institutional ethics committee approved the study protocol, and all participants gave written informed consent.

Diagnostic Criteria for Pleural Effusions

The clinical diagnosis of HF was based on the Framingham criteria,[7] along with the echocardiographic findings and response to conventional drug treatment. Hepatic hydrothorax was defined as a pleural effusion in a cirrhotic patient without an underlying cardiac or pulmonary disease. Parapneumonic effusions were those associated with pneumonia. Tuberculous pleurisy was diagnosed based on the presence of either positive staining findings or a culture of *Mycobacterium tuberculosis* grown in pleural fluid, sputum, or pleural biopsy specimen, or the presence of typical caseating granulomas on the pleural biopsy specimen. A pleural effusion was categorized as malignant if malignant cells were detected on the cytologic examination of the pleural fluid or biopsy specimens. A diagnosis of pulmonary embolism required a positive finding of the spiral CT scan of the chest in the proper clinical setting. Miscellaneous causes of pleural effusion were determined by well-established clinical criteria. The criteria of Light were used to differentiate transudates from exudates.[8]

Biomarker Assays

Laboratory personnel blinded to clinical information performed all commercially available biomarker assays on the stored specimens from the pleural fluid bank. NT-pro-BNP was measured by a monoclonal electrochemiluminescence (ECLIA) immunoassay (Elecsys proBNP II; Roche Diagnostics; Mannheim, Germany) on an analyzer (MODULAR ANALYTICS EVO, E170 module; Roche). The method for testing BNP was a fully automated two-site sandwich immunoassay that makes use of direct chemiluminescent technology (Advia Centaur BNP; Siemens Healthcare Diagnostics; Deerfield, IL). Finally, a sandwich enzyme-linked immunosorbent assay (MBL Medical & Biological Laboratories; Naka-ku Nagoya, Japan) measured the soluble human ST2 protein concentration.

Statistical Analysis

The demographics and laboratory variables were expressed as the medians and interquartile range (IQR). Between-group comparisons of qualitative and quantitative variables were performed with the Fisher exact test and Mann-Whitney *U* test, respectively. The discriminative properties of each biomarker were evaluated using receiver operating characteristic (ROC) curve analysis. For each ROC curve, a cutoff point was determined as the value of the biomarker that maximized the sum of the sensitivity and specificity for diagnosing HF. Pairwise comparisons of the area under the curve (AUC) were conducted, following the procedure of Hanley and McNeil.[9] The 95% confidence intervals (CIs) for the AUC were computed by applying the Bamber-Hanley-McNeil-Wilcoxon-Mann-Whitney nonparametric method; we used the binomial exact CI for sensitivity, specificity, and log-transformed likelihood ratio (LR) data. The linear correlation between the base 10 logarithm of BNP, NT-pro-BNP, and ST2 was evaluated by the Pearson correlation coefficient. A logistic regression analysis was done to determine the relative contribution of gender, age, and serum creatinine level to the identification of HF in a model that already included the natriuretic peptide concentrations. The statistical significance level was set at 0.05 (two tailed). All analyses were conducted using R software (http://www.r-project.org/), a language and environment for statistical computing.[10]

Results

Patients' Characteristics and Distribution of Biomarker Concentrations in Pleural Effusions

We analyzed pleural fluid samples from 90 patients with HF and 91 patients with noncardiac

Table 1—*Baseline Characteristics of 181 Patients With Pleural Effusion*

Characteristics	Cardiac Effusions (n = 90)	Noncardiac Effusions (n = 91)	p Value*
Age, yr	80 (74–83)	61 (41.5–76)	< 0.001
Male gender	44 (49.4)	50 (55)	0.55
Serum creatinine, mg/dL	1.19 (0.92–1.68)	0.81 (0.70–1.14)	< 0.001
PF NT-proBNP, pg/mL	6,203 (3,852–12,761)	348 (127–591)	< 0.001
PF BNP, pg/mL	182 (111–372)	30 (14–72)	< 0.001
PF ST2, ng/mL	0.30 (0.18–0.58)	0.22 (0.08–0.50)	0.04

Data are expressed as the median (IQR) or No. (%), unless otherwise indicated. PF = pleural fluid.
*Calculated using the Fisher exact test for qualitative data and the Mann-Whitney *U* test for quantitative data.

effusions, including 10 hepatic hydrothoraces, 40 malignant effusions, 15 parapneumonic effusions, 11 tuberculous effusions, and 15 miscellaneous exudate effusions (pulmonary embolism, 12 patients; hemothorax, 1 patient; Dressler syndrome, 1 patient; and drug-induced pleural disease, 1 patient). Table 1 lists the characteristics of these two groups. As expected, the patients with HF were of advanced age and more often had acute pre-renal failure. The respective median concentrations of pleural NT-pro-BNP and BNP were significantly higher in patients judged to have HF (6,203 and 182 pg/mL, respectively) than in those patients with noncardiac effusions (348 and 30 pg/mL, respectively; $p < 0.001$). The pleural fluid ST2 levels were also higher in the group with cardiac effusions, but the differences barely reached the level of statistical significance. Figure 1 represents the median values of the three biomarkers according to the specific etiologies.

Operating Characteristics of Pleural Fluid Biomarkers

The ROC analysis demonstrated an AUC of 0.96 (95% CI, 0.94 to 0.99) for pleural fluid NT-pro-BNP, with the following two candidates for the cutoff points: 1,300 and 1,500 pg/mL (Table 2). Comparatively, NT-pro-BNP had a better AUC than BNP (0.90; 95% CI, 0.86 to 0.95; $p = 0.002$) [Fig 2]. The optimal cutoff point for BNP concentration was set at 115 pg/mL, although a value of 75 pg/mL had almost identical accuracy (Table 2). Both natriuretic

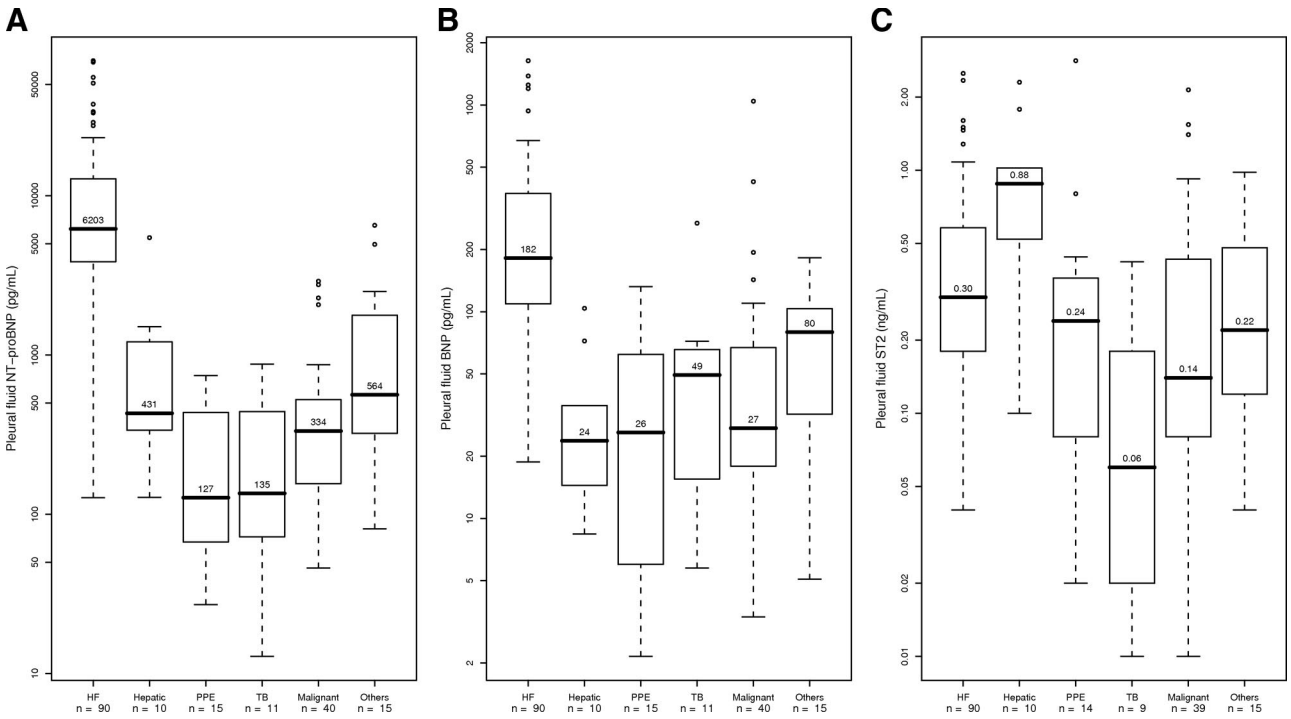

FIGURE 1. Box plot illustrating the distribution of log NT-pro-BNP (*A*), BNP (*B*), and ST2 (*C*) pleural fluid values in patients with different causes of pleural effusion. Box plots represent the median, IQR, and range with outliers plotted separately. PPE = parapneumonic effusion.

Table 2—*Measures of Diagnostic Accuracy for Natriuretic Peptide Tests That Identify a Cardiac Effusion*

PF Biomarkers	Sensitivity, %	Specificity, %	Accuracy, %	LR+	LR−
NT-proBNP, pg/mL					
> 1,300	95.6 (89–98.8)	87.9 (79.4–93.8)	91.7 (86.7–95.3)	7.9 (4.5–13.8)	0.05 (0.02–0.13)
> 1,500	93.3 (86.1–97.5)	89 (80.7–94.6)	91.2 (86–94.9)	8.5 (4.7–15.3)	0.07 (0.03–0.16)
BNP, pg/mL					
> 75	88.9 (80.5–94.5)	76.9 (66.9–85.1)	82.9 (76.6–88.1)	3.8 (2.5–5.9)	0.14 (0.08–0.25)
> 115	74.4 (64.2–83.1)	92.3 (84.8–96.9)	83.4 (77.2–88.5)	9.7 (4.7–19.9)	0.28 (0.19–0.40)

Values in parentheses are 95% CIs. See Table 1 for abbreviation not used in the text.

peptides substantially surpassed the performance characteristics of ST2 (AUC, 0.59; 95% CI, 0.50 to 0.67), which had no discriminating properties at the best cutoff of 0.15 ng/mL (sensitivity, 78% [95% CI, 68 to 86%]; specificity, 42.5% [95% CI, 32 to 54%]; LR positive, 1.35 [95% CI, 1 to 1.7]; and LR negative, 0.52 [95% CI, 0.33 to 0.83]) [Fig 2]. Notably, the median ST2 levels were significantly higher in the 10 patients with hepatic hydrothorax (0.88 ng/mL; IQR, 0.58 to 1.01) than in the patients with other etiologies (0.24; IQR, 0.11 to 0.50; $p < 0.001$), yielding an AUC of 0.80 (95% CI, 0.65 to 0.95) for identifying cirrhosis-associated effusions.

Correlations Between Pleural Fluid Biomarkers

Simple linear regression between the log-transformed concentrations of NT-pro-BNP and BNP demonstrated a positive correlation ($r = 0.78$; $p < 0.001$) [Fig 3], but none of the natriuretic peptides had any linear relationship with ST2. It should be noted that even a coefficient of 0.78 means that only 60% of the variability in NT-pro-BNP can be explained by BNP concentration.

Contribution of Additional Covariates in the Identification of HF-Associated Effusions

When sex, age, and serum creatinine levels, in addition to pleural fluid NT-pro-BNP concentration, were entered into a logistic regression model, they made no significant contribution to the identification of HF-associated effusions. However, sex and age, but not creatinine level, were significant independent contributors to the diagnostic operating characteristics of BNP levels. Therefore, in a model that took these covariates into account, the best discriminatory cutoff values for pleural fluid BNP were as follows: (1) BNP, > 40 pg/mL for women < 75 years of age (sensitivity, 92.3%; specificity, 70%; AUC, 0.88); (2) BNP > 80 pg/mL for women > 75 years of age (sensitivity, 87.1%; specificity, 81.8%; AUC,

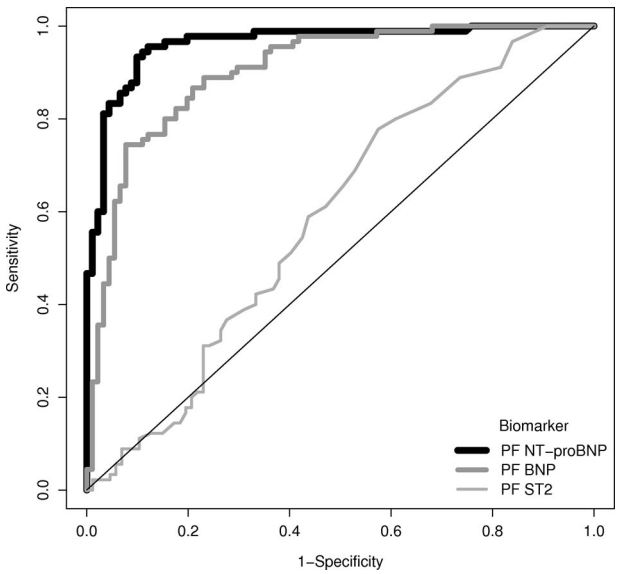

FIGURE 2. ROC curves for pleural fluid (PF) biomarkers. The AUCs were 0.96 (95% CI, 0.94 to 0.99), 0.90 (95% CI, 0.86 to 0.95), and 0.59 (95% CI, 0.50 to 0.67), respectively, for NT-pro-BNP, BNP, and ST2.

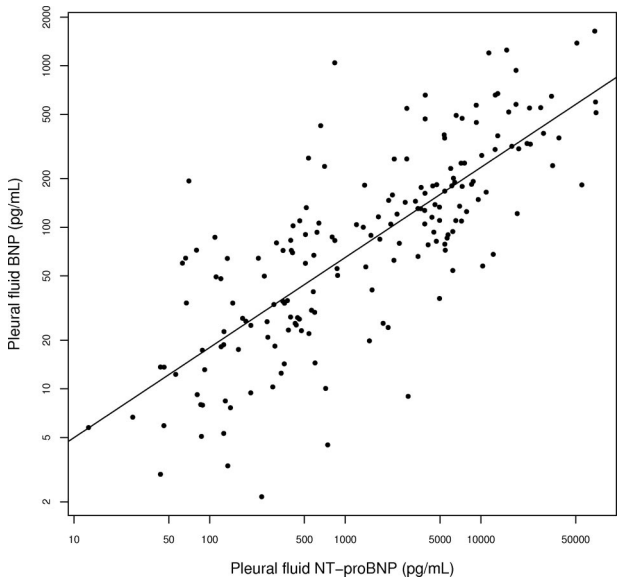

FIGURE 3. Scatterplot of pleural fluid NT-pro-BNP and BNP (log-scale) showing a linear relationship between both biomarkers ($r = 0.78$, $p < 0.001$).

0.90); and (3) BNP > 115 pg/mL in men either < 75 years of age (sensitivity, 76.9%; specificity, 83.8%; AUC, 0.87) or > 75 years of age (sensitivity, 87.1%; specificity, 100%; AUC, 0.98). The AUC in this latter subgroup did not differ significantly from that of NT-pro-BNP concentration (p = 0.16).

Classification of Mislabeled Cardiac Effusions

Of the 20 cardiac effusions misclassified as exudates by the Light criteria, 18 (90%) and 16 (80%) had pleural NT-pro-BNP levels > 1,300 pg/mL and 1,500 pg/mL, respectively; whereas, 18 (90%) and 14 (70%) showed pleural BNP levels above the respective cutoff points of 75 and 115 pg/mL. In contrast, the serum-pleural fluid protein gradient would have correctly labeled only 10 of these effusions (50%). The albumin gradient truly identified 9 of the 12 incorrectly categorized cardiac effusions (75%) for which data were available. None of the false exudative cardiac effusions, as determined by both standard and NT-pro-BNP criteria, would have resulted in true transudates, as determined by either the albumin or protein gradients.

There were six men > 75 years of age with HF whose pleural fluid was categorized as exudate by standard criteria. All of them had pleural NT-pro-BNP concentrations > 1,500 pg/mL, and BNP concentrations > 115 pg/mL, but two patients would have remained falsely classified by the protein gradient.

Discussion

In this study, three quantitative markers of cardiac stress,[4] namely NT-pro-BNP, BNP, and ST2, were measured in pleural fluid, and their concentrations were found to be higher among patients with HF than among those with noncardiac effusions. This is the first report on the use of pleural fluid BNP and ST2 concentrations to determine the cardiac origin of a pleural effusion. On comparing the accuracy of all three tests, the levels of pleural fluid NT-pro-BNP revealed significantly better discriminating properties than those of BNP and ST2 in diagnosing HF. In fact, the latter had no role in the differential diagnosis of pleural effusion. However, additional research about the unexpectedly elevated pleural fluid concentrations of ST2 protein in hepatic hydrothoraces compared with those observed in the other etiologies is needed.

Clinical assessment aids in deciding which patients with pleural effusion most likely have HF, but this judgment has been proven to be inaccurate. In one study[11] of 64 patients with transudates, including 44 caused by HF, the initial clinical presumption failed to categorize the effusion correctly in approximately 40% of cases. The Light criteria[8] were better, but 25% of transudates were still mislabeled. Therefore, there is a need for a more accurate test to reduce the number of misclassified cardiac effusions for which further testing is required. Notably, NT-pro-BNP testing revealed 40% more false cardiac exudates than did the serum-to-pleural protein gradient.

The performance characteristics of natriuretic peptides in diagnosing the cardiac etiology of pleural effusions have been the subject of a few publications,[6,12–18] which are tabulated in Table 3. There is general agreement on the high discriminative value of pleural fluid or serum NT-pro-BNP levels, albeit with different threshold levels. Herein, we have confirmed the results of our two previous investiga-

Table 3—*Studies on Natriuretic Peptides for the Identification of Cardiac Effusions*

Study/Year	Cardiac/ Noncardiac Effusions, No.	PF or S NP Cutoffs, pg/mL	Sensitivity, %	Specificity, %	AUC	Misclassified Cardiac Effusions, No. (%)*	No. (%) of Misclassified Cardiac Effusions With High NP Levels
Porcel et al[12]/2004	44/73	PF NT-proBNP > 1,500	91	93	0.97	10 (28.5)	8 (80)
Tomcsányi et al[13]/2004	14/14	PF or S NT-proBNP > 599	100	100	ND	1 (7)	1 (100)
Gegenhuber et al[14]/2005	31/26	Plasma BNP > 520	97	89	0.97	10 (32)	9 (90)
Kolditz et al[15]/2006	25/68	PF NT-proBNP > 4,000	92	93	0.98	9 (36)	9 (100)
		S NT-proBNP > 4,000	88	93			9 (100)
Porcel et al[6]/2007	53/40	PF NT-proBNP > 1,500	92	87	0.93	8 (15)	6 (75)
		S NT-proBNP > 1,500	92	85	0.92		6 (75)
Liao et al[16]/2008	10/30	PF NT-proBNP > 2,220	100	96.7	0.99	ND	ND
Han et al[17]/2008	82/158	PF NT-proBNP > 1,714	99	99	0.99	28 (34)	27 (96)
Seyhan et al[18]/2009	51/64	PF NT-proBNP > 1,092	92	95	0.97	17 (33)	17 (100)
		S NT-proBNP > 1,150	90	95	0.96		16 (94)
Current series	90/91	PF NT-proBNP > 1,300	96	88	0.96	20 (22)	18 (90)
		PF BNP > 115	74	92	0.90		14 (70)

ND = not done; NP = natriuretic peptide; S = serum. See Table 1 for abbreviation not used in the text.
*Effusions that met the Light criteria for exudates.

tions[6,12] in that a pleural fluid NT-pro-BNP level > 1,500 pg/mL is almost diagnostic that the patient has HF. However, the adoption of 1,300 pg/mL as a cutoff value for NT-pro-BNP resulted in a better classification of the false cardiac exudates, without compromising the overall diagnostic accuracy. In the present study, we used a second-generation ECLIA, which substitutes two new monoclonal antibodies for polyclonal antibodies. The monoclonal ECLIA method has shown very similar analytical characteristics with slightly lower NT-pro-BNP results (on average, −2.5%) than the first-generation polyclonal ECLIA method[19] that was used in our previous series.[6,12]

As expected, we demonstrated a good correlation between NT-pro-BNP and BNP, where a high pleural fluid BNP level (> 115 pg/mL) also makes the diagnosis of HF extremely likely. Although NT-pro-BNP and BNP shared a clinically relevant diagnostic accuracy in HF patients, the first outperformed the latter according to the comparison of their AUC. The exception was the subgroup of men > 75 years of age, for whom both natriuretic peptides showed similar operating characteristics. Technically, BNP and NT-pro-BNP are both fully automated methods, but the latter is more stable *in vitro* than the former and, therefore, can be performed not only in ethylenediaminetetraacetic acid samples (as for BNP) but also in serum or heparinized samples.[1,2] Taken together, our results advocate choosing NT-pro-BNP, based on its impressive test characteristics (AUC, 0.96), rather than BNP to substantiate the diagnosis of HF-associated effusions.

Natriuretic peptide levels may be influenced by several patient factors, including age, sex, renal function, thyroid function, anemia, and body habitus.[20,21] We found that the cutoff concentrations of pleural fluid BNP depended on the age and gender of the population. Thus, the BNP threshold values should be lowered in women, particularly in those < 75 years old, in order to increase the sensitivity for predicting HF. Nevertheless, we could not confirm any major contribution of serum creatinine, a less than perfect measure of renal function, to natriuretic peptide levels.

Our study has several potential limitations. First, we limited our study population to patients with well-defined causes of pleural effusion, thus excluding those in whom a definitive diagnosis could not be established. This study design may somewhat overestimate the ROC curves, but it is the first step to prove the validity of a diagnostic test. Second, we did not evaluate natriuretic peptides in serum or plasma, although according to previous reports, we can assume they might be as accurate as in pleural fluid, at least concerning NT-pro-BNP measurements.[6,15] Third, we ignore to what extent natriuretic peptide tests add diagnostic information to the physician's initial clinical impression. However, because the Light criteria proved to be better than the clinician's judgment in identifying transudates in one study,[11] and we have demonstrated the value of NT-pro-BNP to categorize the misclassified cardiac effusions correctly by the Light criteria, a plausible inference is that this test probably provides diagnostic utility beyond clinical data. Similarly, whether NT-pro-BNP testing in pleural fluid results in cost savings in the diagnosis of cardiac effusions is a matter of speculation, although cost effectiveness is the most likely if the NT-pro-BNP application is limited to those cases where the Light criteria are not contributory. Finally, we did not adjust natriuretic peptide concentrations for body mass index, glomerular filtration rate, hemoglobin, or the use of diuretics. It should be noted, however, that the confounding effects of the different clinical factors are less apparent in the setting of acute exacerbation of HF,[1] as in the present study.

In conclusion, unlike ST2, natriuretic peptides, and, more specifically, NT-pro-BNP are powerful and accurate biochemical markers for diagnosing HF-associated effusions. Nevertheless, until more data are available on how these markers should be integrated into clinical care, their routine use in patients with an obvious diagnosis of HF is not warranted. Rather, NT-pro-BNP measurements should be limited to cases in which the cause of the pleural effusion remains uncertain after the standard clinical assessment. More importantly, the use of the NT-pro-BNP levels may overcome the problem of misclassified cardiac effusions by the Light criteria substantially better than the recommended serum-to-pleural fluid protein gradient.

Acknowledgments

Author contributions: Conception and design: Drs. Porcel and Esquerda, Ms. Martínez-Alonso. Analysis and interpretation of the data: Ms. Martínez-Alonso and Dr. Bielsa. Drafting of the article: Dr. Porcel. Critical revision of the article for important intellectual content: Drs. Porcel, Cao, Bielsa, Sopena, and Esquerda, and Ms. Martínez-Alonso. Final approval of the article: Drs. Porcel, Cao, Bielsa, Sopena, and Esquerda, and Ms. Martínez-Alonso. Statistical expertise: Ms. Martínez-Alonso. Collection and assembly of data: Drs. Porcel, Bielsa, and Esquerda. Measurement of biomarkers: Drs. Cao, Sopena, and Esquerda.
Financial/nonfinancial disclosures: The authors have reported to the ACCP that no significant conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

References

1 Tang WH, Francis GS, Morrow DA, et al. National Academy of Clinical Biochemistry Laboratory Medicine practice guide-

lines: clinical utilization of cardiac biomarker testing in heart failure. Clin Biochem 2008; 41:210–221
2 Porcel JM. The use of probrain natriuretic peptide in pleural fluid for the diagnosis of pleural effusions resulting from heart failure. Curr Opin Pulm Med 2005; 11:329–333
3 Porcel JM. Establishing a diagnosis of pleural effusion due to heart failure. Respirology 2007; 12:654–659
4 Braunwald E. Biomarkers in heart failure. N Engl J Med 2008; 358:2148–2159
5 Rehman SU, Mueller T, Januzzi JL Jr. Characteristics of the novel interleukin family biomarker ST2 in patients with acute heart failure. J Am Coll Cardiol 2008; 52:1458–1465
6 Porcel JM, Chorda J, Cao G, et al. Comparing serum and pleural fluid pro-brain natriuretic peptide (NT-proBNP) levels with pleural-to-serum albumin gradient for the identification of cardiac effusions misclassified by Light's criteria. Respirology 2007; 12:654–659
7 Kapoor JR, Perazella MA. Diagnostic and therapeutic approach to acute decompensated heart failure. Am J Med 2007; 120:121–127
8 Light RW. Pleural effusion. N Engl J Med 2002; 346:1971–1977
9 Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology 1983; 148:839–843
10 R Development Core Team 2008. R: a language and environment for statistical computing. Available at: http://www.R-project.org. Accessed July 18, 2009
11 Romero-Candeira S, Hernández L, Romero-Brufao S, et al. Is it meaningful to use biochemical parameters to discriminate between transudative and exudative pleural effusions? Chest 2002; 122:1524–1529
12 Porcel JM, Vives M, Cao G, et al. Measurement of pro-brain natriuretic peptide in pleural fluid for the diagnosis of pleural effusions due to heart failure. Am J Med 2004; 116:417–420
13 Tomcsányi J, Nagy E, Somlói M, et al. NT-brain natriuretic peptide levels in pleural fluid distinguish between pleural transudates and exudates. Eur J Heart Fail 2004; 6:753–756
14 Gegenhuber A, Mueller T, Dieplinger B, et al. Plasma B-type natriuretic peptide in patients with pleural effusions: preliminary observations. Chest 2005; 128:1003–1009
15 Kolditz M, Halank M, Schiemanck CS, et al. High diagnostic accuracy of NT-proBNP for cardiac origin of pleural effusions. Eur Respir J 2006; 28:144–150
16 Liao H, Na MJ, Dikensoy O, et al. Diagnostic value of pleural fluid N-terminal pro-brain natriuretic peptide levels in patients with cardiovascular diseases. Respirology 2008; 13:53–57
17 Han CH, Choi JE, Chung JH. Clinical utility of pleural fluid NT-pro brain natriuretic peptide (NT-proBNP) in patients with pleural effusions. Intern Med 2008; 47:1669–1674
18 Seyhan EC, Altin S, Cetinkaya E, et al. The importance of pleural fluid and serum NT-proBNP levels in differentiating pleural effusion due to heart failure from other causes of effusion. Intern Med 2009; 48:287–293
19 Prontera C, Zucchelli GC, Vittorini S, et al. Comparison between analytical performances of polyclonal and monoclonal electrochemiluminescence immunoassays for NT-proBNP. Clin Chim Acta 2009; 400:70–73
20 Rehman SU, Januzzi JL Jr. Natriuretic peptide testing in clinical medicine. Cardiol Rev 2008; 16:240–249
21 Ordonez-Llanos J, Collinson PO, Christenson RH. Amino-terminal pro-B-type natriuretic peptide: analytic considerations. Am J Cardiol 2008; 101:9–15