Clinical Utility of Pleural Fluid NT-pro Brain Natriuretic Peptide (NT-proBNP) in Patients with Pleural Effusions

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Abstract

Background Pleural effusion is not a pathognomonic sign and distinguishing between transudates and exudates often presents a diagnostic dilemma.

Objective To examine whether the NT pro-brain natriuretic peptide (NT-proBNP) in pleural fluid is a diagnostic tool for determining the cardiac etiology of pleural effusions.

Methods We measured pleural fluid and serum NT-proBNP levels in a consecutive series of 98 patients with heart failure and in 142 patients with other causes.

Results The median pleural fluid NT-proBNP levels among the heart failure patients were significantly higher (3,310 pg/mL) than hepatic hydrothorax (16 patients, 531 pg/mL), malignant pleural effusion (38 patients, 733 pg/mL), parapneumonic pleural effusion (40 patients, 294 pg/mL), and tuberculous pleural effusion (64 patients, 214 pg/mL) ($p < 0.001$). At a cut-off point of $\geq 1,714$ pg/mL, the test had a sensitivity of 99%, a specificity of 99 % for the diagnosis of heart failure. There were 28 patients with pleural effusion due to heart failure misclassified as exudates by Light's criteria. Ten cases of misclassified heart failure (36% of 28 patients) showed serum-effusion protein gradient less than 3.1 g/dL; 26 of them exhibited pleural fluid NT-proBNP levels of $\geq 1,714$ pg/mL. The 26 patients of misclassified heart failure received diuretics before thoracentesis. Pleural fluid NT-proBNP levels were correlated with serum NT-proBNP levels ($R^2 = 0.928$, $p < 0.001$).

Conclusion Pleural fluid NT-proBNP may be useful in the diagnosis of pleural effusion resulting from heart failure. The test may be especially useful in heart failure patients with exudates who have been treated with diuretics.

Key words: natriuretic peptides, pleural effusion, transudates, heart failure

(Inter Med 47: 1669-1674, 2008)

(DOI: 10.2169/internalmedicine.47.1276)

Introduction

The classification of pleural fluid as a transudate or an exudate simplifies diagnostic efforts in determining the cause of pleural effusions. Multiple pleural fluid tests are available to discriminate between these two classes of effusion. The usefulness of biochemical criteria to separate pleural transudates from exudates is controversial, and the limitations of Light's criteria in patients receiving diuretic therapy are of general concern. The use of Light's criteria to differentiate transudates from exudates has been generally

accepted as a first step in the study of patients with pleural effusion (1). Using Light's criteria, 20% to 30% of transudates are misclassified as exudates. Apart from the potential presence of unsuspected exudative disease, most cases of false exudative effusion by Light's criteria occur in patients receiving diuretic therapy (2).

Amino-terminal brain natriuretic peptide precursor (NT-proBNP) is a member of vasoactive peptides produced from the heart. NT-proBNP measured in serum is a convenient tool for heart failure but little is known about the utility of pleural fluid NT-proBNP.

Therefore we evaluated the effectiveness of NT-proBNP

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Received for publication May 2, 2008; Accepted for publication June 25, 2008

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in pleural fluid as a diagnostic tool for determining the cardiac etiology of pleural effusions.

Methods

Study population and diagnostic evaluation

Two hundred and forty patients who visited our hospitals with pleural effusions between January, 2006 and December, 2006 were studied prospectively. For this study, only diagnostic thoracentesis was considered, and when more than one was performed, only the first data was used.

Pleural fluid and serum samples were obtained. Biochemical analysis, bacterial and fungal culture, acid-fast bacilli smear, PCR for *Mycobacterium tuberculosis*, and cytologic examinations were performed on all pleural fluid samples. Further investigations, such as pleural biopsy, were performed at the discretion of the primary physicians.

Measurement of NT-proBNP levels in serum and pleural effusion and all other biochemical analyses were carried out within four hours after specimen collection. NT-proBNP was measured by electrochemiluminescence immunoassay using the Elecsys 2010 (Roche Diagnostics, Barcelona, Spain) according to the manufacturer's protocol. The test has an intra-assay co-efficient of variation of 0.8% to 3%, and a detection range from 5 to 35,000 pg/mL.

Pleural effusions were categorized as either exudates or transudates according to the criteria of Light et al (1). The fluid was defined as exudates if it fulfilled at least one of the following criteria: pleural/serum ratio of total protein greater than 0.5; pleural/serum ratio of total lactate dehydrogenase greater than 0.6; or pleural lactate dehydrogenase greater than two-thirds of upper limit of normal for serum lactate dehydrogenase (i.e., >400 IU/L).

Pleural effusion was attributed to heart failure when the patient had symptoms and signs of the left ventricular failure, echocardiography study revealed systolic or diastolic dysfunction of the left ventricle, and the pleural effusion responded to appropriate therapy.

Hepatic hydrothorax was defined as an effusion due to cirrhosis in the presence of ascites.

Malignant pleural effusion was diagnosed if the pleural fluid cytology or pleural biopsy findings were positive, or if the patient had a persistent pleural effusion and a known malignancy and alternative diagnoses were excluded. Parapneumonic pleural effusion was defined as the clinical and radiological diagnosis of pneumonia or positive bacterial culture in pleural fluid. Pleural fluid was categorized as tuberculous if *Mycobacterium tuberculosis* were found in pleural fluid or granuloma in pleural biopsy or an exudative lymphocytic effusion with high adenosine deaminase levels (>40 U/L) cleared in response to antituberculous therapy. Other diagnoses were established based on clinical and laboratory data.

Table 1. Causes of Pleural Effusions

Etiology	Patients, No.
Transudates	98
Congestive heart failure	82
Liver cirrhosis	16
Exudates	142
Tuberculosis	64
Parapneumonic	40
Malignant	38

Exclusion criteria

The following were excluded in the analyses: effusions of undetermined origin, effusions with more than one possible cause, empyema, and hemothorax. NT-proBNP levels are known to increase with age, female sex, and renal function hence we excluded renal failure (serum creatinine >1.4 mg/dL).

Other diagnoses were established based on clinical and laboratory data.

Statistical analysis

Values are reported as the median (25th and 75th percentiles) since they were found not to be normally distributed. Mann-Whitney U test or Fisher exact test were used to assess the difference between different groups. The Spearman coefficient of rank correlation was used to assess the relation of plasma and pleural fluid NT-proBNP. To determine the diagnostic accuracy of NT-proBNP for heart failure, receiver operating characteristic (ROC) curve was analyzed and the area under curve (AUC) was calculated. Cut-off levels for pleural fluid NT-proBNP were derived from the ROC curve. A p-value of 0.05 or less was regarded as significant. For statistical analysis, a statistical software package (SPSS, version 12.0; SPSS Inc; Chicago, IL; and MedCalc, version 9.5.2.0; MedCalc software; Mariakerke, Belgium) was applied.

Results

Two hundred and fifty consecutive patients presenting for thoracentesis, 166 men and 74 women, were examined in the study. Ten patients were excluded from the study, including 4 patients with a diagnosis of empyema, 6 patients with pleural effusions due to multiple superimposed diseases. The median age of the 240 study patients was 65 years. The diagnoses are listed in Table 1. Ninety-eight were defined as transudates and 142 as exudates.

Median levels of pleural fluid NT-proBNP among patients with heart failure were significantly higher (3,310 pg/mL) than those patients with hepatic hydrothorax (531 pg/mL), malignant pleural effusions (733 pg/mL), tuberculous pleural effusions (214 pg/mL), and parapneumonic pleural effusions

(294 pg/mL)(Fig. 1, Table 2).

Levels of NT-proBNP measurement in pleural and in serum were closely correlated (Spearman's coefficient of rank correlation 0.928; $p < 0.001$; Fig. 2).

Using the criteria of Light et al (1), 38 effusions were incorrectly classified (16%). Thirty-two were transudates (33% of the 98 transudates, 28 patients; heart failure, 4 patients; hepatic hydrothorax) and 4 were exudates (4% of the 142 exudates). Characteristics of twenty-eight patients with pleural effusion due to heart failure misclassified as exudates by Light's criteria are shown in Table 3. Ten cases with pleural effusion due to heart failure misclassified as exudates by Light's criteria (36% of 28 patients) showed serum-effusion protein gradient less than 3.1 g/dL. Twenty-seven of them exhibited pleural fluid NT-proBNP levels of $\geq 1,714$ pg/mL.

Figure 1. The median and quartiles of pleural NT-proBNP values according to transudates by clinical diagnosis.

One of the 28 patients with misclassified heart failure had a pleural fluid NT-proBNP level of 1,535 pg/mL.

Twenty-eight cases of misclassified transudates (26 patients; heart failure, 2 patients; hepatic hydrothorax) received diuretics before thoracentesis.

As determined by ROC curve analysis (Fig. 3), an NT-proBNP cut-off value of 1,714 pg/mL in pleural fluid had a sensitivity of 95% (95% confidence interval [CI]: 93% to 100%), a specificity 99% (95% CI: 96% to 100%) for heart failure cases. Table 4 gives detailed diagnostic information, including the appropriate decision statistics for the biochemical diagnosis of pleural effusions caused by heart failure.

Figure 2. Correlation of serum and pleural effusion level of NT-proBNP. Spearman's coefficient of rank correlation is 0.928 ($p < 0.001$).

Table 2. Characteristics of Study Populations

	Heart Failure (n=82)	Hepatic Hydrothorax (n=16)	Exudates (n=142)	p-value*
Age (years)	66(59-71) [†]	65(52-69)	64 (50-70)	0.06
Male/Female	58/24	14/2	94/48	0.71
Pleural fluid protein (g/L)	2.2 (1.6-2.5) [†]	2.4 (2.0-2.5) [†]	4.3 (3.0-4.9)	<0.001
Pleura/Serum protein ratio	0.35 (0.29-0.45) [†]	0.40 (0.35-0.42) [†]	0.65 (0.52-0.75)	<0.001
Pleural fluid LDH (IU/L)	167 (137-210) [†]	171 (148-307) [†]	567 (360-755)	<0.001
Pleura/Serum LDH ratio	0.48 (0.34-0.58) [†]	0.50 (0.41-0.87) [†]	1.04 (0.83-1.69)	<0.001
Serum NT-proBNP (pg/mL)	3308 (2347-4978) [†]	498 (380-673)	294 (115-786)	<0.001
Pleural fluid NT-proBNP (pg/mL)	3310 (2638-4129) [†]	531(401-768)	267 (115-756)	<0.001

Data are presented as median (interquartile range), LDH, lactate dehydrogenase; NT-proBNP, N-terminal-pro-B-type natriuretic peptide. *Comparing patients who had heart failure with the remaining patients. [†]Significantly different compared with exudates.

Table 3. Characteristics of Patients with Pleural Effusion Due to Heart Failure Misclassified as Exudative by Light's Criteria

	n=28
Age	65 (59-67)
Male/Female	19/9
Serum to pleural protein gradient ≥ 3.1 g/dL	18 (64%)
Pleural fluid NT-proBNP ≥ 2000 pg/mL	26 (93%)
Pleural fluid protein (g/L)	2.2 (1.6-2.9)
Pleura/Serum protein ratio	0.37 (0.26-0.54)
Serum to pleura protein gradient (g/dL)	3.9 (2.6-4.6)
Pleural fluid LDH (IU/L)	265 (190-382)
Pleura/Serum LDH ratio	0.58 (0.38-0.68)
Serum NT-proBNP (pg/mL)	4265 (3401-5630)
Pleural fluid NT-proBNP (pg/mL)	4778 (3633-6360)

Data are presented as median (interquartile range), LDH, lactate dehydrogenase; NT-proBNP, N-terminal-pro-B-type natriuretic peptide.

Figure 3. Receiver operating characteristic curve of N-terminal-pro-B-type natriuretic peptide (NT-proBNP) levels in pleural effusion for differentiating between heart failure and other causes. The AUC (area under curve) for pleural fluid NT-proBNP was 0.996 (95% confidence interval 0.990-1.003).**Table 4.** Diagnostic Information for Pleural Fluid NT-proBNP Concentration in the Diagnosis of Pleural Effusion Caused by Heart Failure

Pleural fluid NT-proBNP cut-off concentration (pg/mL)	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value	Diagnostic accuracy %
1535	99 (93-99)	94 (89-97)	88 (81-94)	99 (96-100)	95
1714	99 (93-100)	99 (96-100)	99 (93-100)	99 (97-100)	99
3089	52 (41-64)	99 (96-100)	97 (86-100)	82 (76-84)	85

Discussion

Light's criteria for differentiating exudates from transudates has been widely accepted. However, Light's criteria may lead to unwarranted invasive interventions in 20-30%

of patients with transudates (3, 4). This casts some doubt on the universal applicability of these criteria. Several other methods have been proposed to differentiate exudates from transudates, including the serum-effusion albumin gradient (3), serum-effusion protein gradient, pleural cholesterol concentration (5), and pleural effusion/serum bilirubin ratio (6).

The tests that have been proposed to indicate a pleural exudates have included a pleural cholesterol greater than 60 mg/dL (5), a gradient of less than 1.2 g/dL for the difference in the pleural fluid and serum albumin level (3), a pleural fluid-to-serum bilirubin ratio above 0.6 (6). Controversy exists as to which method is more accurate and effective.

Diuretic treatment is a possible explanation for biochemical exudates for heart failure. Diuretics may change a transudate into an exudate by shifting fluid from pleural space, thereby elevating the pleural levels of protein and lactate dehydrogenase (7, 8).

B-type natriuretic peptide (BNP) is a vasoactive neurohormone that is produced by the heart. The synthesis of these peptides is augmented by the increased wall tension or stretch of cardiac chambers. The FDA has cleared both BNP and NT-proBNP assays to facilitate the diagnosis and assessment of the severity of heart failure and for risk stratification of patients with acute coronary syndrome.

There are several determinants for BNP and NT-proBNP concentrations. It has been shown consistently in several studies that BNP and NT-proBNP are related to sex, with higher values in females, and to age, with higher values in older individuals. The sex relation is thought to be caused by differences in metabolism, whereas the association with age might reflect preclinical structural and functional myocardial alterations not detectable by current techniques.

In patients with reduced renal function, BNP and NT-proBNP values are increased with a negative correlation to creatinine clearance.

Additional diagnostic tests, such as pleural fluid BNP and NT-proBNP measurements have been published supporting the diagnostic tool for determining the etiology of pleural effusions (9-12).

We found out that pleural fluid NT-proBNP levels were significantly higher in patients with effusion due to heart failure as in other reports (9-12). Porcel et al (9) retrospectively examined 117 patients with pleural effusion, of whom 44 (38%) were diagnosed as having pleural effusion due to heart failure. The pleural fluid levels of NT-proBNP were significantly higher in patients with cardiac transudates than in patients with effusion of other causes. At a cut-off of 1,500 pg/mL, pleural fluid NT-proBNP level had a sensitivity of 91% and a specificity of 93% in the diagnosis of heart failure with pleural effusion. The pleural fluid NT-proBNP or BNP cut-off values for discriminating pleural effusion with heart failure are variable from 1,176 pg/mL to 4,000 pg/mL (9-12). We found the pleural fluid NT-proBNP concentration of 1,714 pg/mL to have a good accuracy for detecting pleural effusion with heart failure.

NT-proBNP may provide prognostic information superior to that obtained from BNP (13, 14). Among the past 4 studies (9-12), two were studied using NT-proBNP. In the present NT-proBNP was used.

In agreement with previously reported data (11, 12), the present study shows the close correlation between NT-proBNP levels in pleural fluid and serum. Pleural fluid NT-

proBNP is derived from cardiac ventricular myocytes. Due to its small size (8.5 kd), the peptide can easily diffuse from the blood into the pleural space. Because there is no evidence that NT-proBNP is synthesized by the mesothelial cells, we assume that pleural NT-proBNP levels are proportional to serum NT-proBNP levels. Therefore, Gegenhuber et al (10) claimed that it may not be necessary to perform diagnostic thoracentesis in patients with serum NT-proBNP concentrations exceeding the cut-off value making the diagnosis of heart failure as the underlying cause of the pleural effusion in these patients. However, in all other patients with serum NT-proBNP concentrations below the cut-off value, early diagnostic thoracentesis may be necessary to determine whether the effusion is exudative or transudative in nature. Further studies will clarify this possibility; such as evaluating patients with pleural effusion randomized to check and not check serum NT-proBNP, and to compare the perceived need for thoracentesis in the two groups; postponing diagnostic thoracentesis until a trial of diuretic therapy has been performed when serum NT-proBNP concentrations exceed the cut-off value. This strategy should be addressed in further prospective trials.

We enrolled only diagnostic thoracentesis into the study while Kolditz et al (11) enrolled diagnostic and therapeutic thoracentesis into their study. The reason being by enrolling therapeutic thoracentesis, it may be biased in terms of disease prevalence and diagnostic accuracy of pleural fluid NT-proBNP results. We studied relatively large numbers of patients compared to other studies (9-12).

In patients with heart failure on diuretic therapy, the serum to pleural protein gradient does not increase diuresis. Thus Romeo-Candeira et al (15) asserted that if pleural fluid meets exudative Light's criteria but the effusion is thought to be due to heart failure, the serum to pleural fluids should be examined. And if this gradient is greater than 3.1 g/dL, the pleural fluid in all probability is due to heart failure and additional diagnostic studies are not indicated. But our study showed that pleural fluid NT-proBNP is more accurate than protein gradient.

The use of NT-pro-BNP in the diagnostic assessment and subsequent management of patients could lead to improved patient care while providing substantial cost savings to the health care system. The cost-effectiveness of NT-pro-BNP could reduce the use of echocardiography by up to 58%, prevent 13% of initial hospitalizations, and reduce hospital days by 12% (16).

Our results suggest that the inclusion of pleural fluid NT-proBNP measurement in thoracentesis would enhance discrimination among the different causes of pleural effusion especially for congestive heart failure cases. The test may be especially useful in heart failure patients with exudates who have been treated with diuretics for discriminating between cardiac and hepatic transudates.

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