Pleural Fluid B-Type Natriuretic Peptide Level as an Additional Indicator for the Fluid's Etiology

Ronen Zalts MD[1]*, Tomer Twizer MD[1]*, Ronit Leiba BsC[2] and Amir Karban MD[1]

[1]Departments of Internal Medicine C and [2]Quality of Care Unit, Rambam Health Care Campus, Haifa, affiliated with Rappaport Faculty of Medicine, Technion–Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** The identification of the etiology of a pleural effusion can be difficult. Measurement of serum B-type natriuretic peptide (BNP) levels is helpful in the diagnosis of congestive heart failure (CHF) as a cause of respiratory failure, but pleural fluid BNP measurement is still not part of the workup for pleural effusion.

Objectives: To identify the correlation between pleural fluid BNP levels and clinical diagnosis.

Methods: In this cross-sectional study, data from 107 patients admitted to the department of internal medicine between November 2009 and January 2015 were obtained from medical records. Patients underwent a diagnostic thoracocentesis as part of their evaluation. They were grouped according to final diagnosis at discharge and clinical judgment of the attending physician.

Results: Serum BNP levels were significantly higher in the CHF patients compared to patients with non-cardiac causes of pleural effusion (1519.2 and 314.1 respectively, $P < 0.0001$). Mean pleural fluid BNP was also significantly higher in the CHF patients (1063.2 vs. 208.3, $P < 0.0001$). Optional cutoff points to distinguish between cardiac and non-cardiac etiology of pleural effusion were 273.4 pg/ml (sensitivity 83.3%, specificity 72.3%, accuracy 76.7%) or 400 pg/ml (sensitivity 78.6%, specificity 86.2%, accuracy 83.0%). A strong correlation was found between serum BNP and pleural fluid BNP levels.

Conclusions: High levels of serum BNP in patients presenting with pleural effusion suggest CHF. In cases with doubt regarding the etiology of pleural effusion, high levels of pleural fluid BNP can support the diagnosis, but are not superior to serum BNP levels.

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KEY WORDS: B-type natriuretic peptide (BNP), congestive heart failure (CHF), etiology, pleural effusion, thoracocentesis

Pleural effusion occurs when fluid collects between the parietal and visceral pleura. The accumulation of pleural fluid is associated with a variety of diseases. In clinical practice, pleural effusion is categorized as either transudate or exudate. Transudate is usually caused by heart failure, liver cirrhosis, or nephrotic syndrome. Exudate can be caused by many etiologies such as pneumonia, malignancy, or non-infectious inflammatory diseases. The decision whether the pleural fluid is transudate or exudate is done according to protein or lactate dehydrogenase (LDH) levels in pleural fluid in relation to their levels in the plasma, known as Light's criteria [1]. However, in daily practice it is not uncommon to encounter patients with pleural effusion in which the etiology is unclear, either because of misclassification of the pleural fluid or because of conditions where there is long-standing pleural effusion. In these cases, the pleural fluid characteristics meet exudative criteria according to Light's criteria, but the clinical suspicion is of transudate etiology. Other tests that are routinely recommended on exudative pleural fluid are gram stain and culture, cell count and differential, glucose, amylase, and cytology [2]. These tests are usually conducted to diagnose the etiology for the exudative pleural effusion.

There is growing consensus for the measurement of plasma B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) as markers for heart failure in the evaluation and management of acute dyspnea. The American Heart Association recommends the use of serum BNP or NT-proBNP to support clinical judgment for the diagnosis or exclusion of heart failure, especially in cases in which the etiology of acute dyspnea are unclear [3-5]. The accepted two cut-points for blood BNP measurements in the workup of acute dyspnea are 100 and 400 pg/ml. When blood BNP is low (< 100 pg/ml), congestive heart failure (CHF) is unlikely. However, blood BNP > 400 pg/ml makes CHF the probable diagnosis. The range between 100 and 400 pg/ml is undetermined [6]. In recent years, measurement of pleural fluid natriuretic peptides was suggested as an additional diagnostic tool in the workup of patients with pleural effusion. Studies that investigated levels of pleural fluid BNP and NT-proBNP found these markers very useful in establishing the diagnosis of heart failure associated effusions [7-9]. However, meta-analyses performed found that pleural fluid BNP levels might be inferior to pleural fluid NT-proBNP levels [10,11].

*The first and second authors contributed equally to this study

The aim of this study was to identify the correlation between pleural fluid BNP levels and clinical diagnosis, and to determine whether pleural fluid BNP has any advantage over blood BNP levels.

PATIENTS AND METHODS

In this cross-sectional study, patients admitted to the department of internal medicine between November 2009 and January 2015 with pleural effusion were included. Fluid samples were collected as part of the regular workup of pleural effusion. The fluid was sent to the laboratory immediately after thoracocentesis. The routine measurements of pleural fluid included total protein level, lactate dehydrogenase (LDH), white blood cell count, pH level, glucose, and cytology analysis, and microbiology specimen. A separate 2 ml tube containing ethylenediamine tetraacetic acid (EDTA) was sent to the laboratory to measure BNP levels. Blood levels of BNP were sent to the laboratory according to the physician's decision, as an aid, in cases in which the clinical diagnosis was unclear. Light's criteria were used to classify the pleural effusion as exudate or transudate.

A pleural fluid was defined as an exudate when one or more of Light's criteria were positive:

- Pleural fluid/serum protein ratio > 0.5
- Pleural fluid/serum LDH ratio > 0.6
- Pleural fluid LDH level > 2/3 of the normal upper limit for serum [12]

The final diagnosis at discharge was conducted according to the clinical judgment of the attending physician. Additional diagnostic tests included echocardiograph, ultrasound, and computed tomography scan, among others. The study was approved by the ethics committee at Rambam Health Care Campus.

STATISTICAL ANALYSIS

The demographic and clinical variables were expressed as median, average, and standard deviation. Fisher's exact test was used to compare qualitative variables between groups, and the Mann–Whitney U test was used for quantitative variables. Correlation between two quantitative measures was performed with Spearman's correlation coefficient. The discriminative property of BNP was evaluated using receiver operating characteristic (ROC) curve analysis. A logistic regression analysis was conducted to determine the predictability of blood levels of BNP and pleural fluid determination in identification of heart failure. $P < 0.05$ was considered as statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 21 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

The study comprised 107 patients. Sixty-one had exudative pleural effusion and 45 were diagnosed as transudate, according to Light's criteria. One patient had no definition of pleural fluid. The final diagnosis in 42 patients (39.3%) was CHF. Fifty-seven (53.3%) showed pleural effusion originating from non-cardiac causes (mainly cancer-related and para-pneumonic effusions). Eight patients (7.5%) expressed transudate because of nephrotic syndrome and cirrhosis. Patients were categorized into three groups according to the final diagnosis. The mean pleural fluid/serum protein ratio in the group of patients with CHF was 0.38 pg/ml compared to 0.6 in patients with non-cardiac causes ($P < 0.0001$). The mean pleural fluid/serum LDH ratio was 0.47 in the CHF group and 4.9 in the non-cardiac group ($P < 0.0001$). Blood BNP levels were significantly higher in the CHF patient compared to patients with non-cardiac causes of pleural effusion (1519.2 ± 1121.6 pg/ml and 314.1 ± 470.2 pg/ml, respectively, $P < 0.0001$). Mean pleural fluid BNP was also significantly higher in the CHF patients (1063.2 ± 986.9 pg/ml vs. 208.3 ± 214.6 pg/ml, $P < 0.0001$). Forty-three patients had severe infection during the admission period. The demographic and clinical characteristics of patients are summarized in Table 1.

The ROC analysis for pleural fluid BNP, plotted as the true positive rate (patients with pleural effusion diagnosed with CHF) against the false positive rate demonstrated an area under

Table 1. Main demographic and clinical characteristics of patients

	CHF (n=42)	Other causes of transudate (n=8)	Non-cardiac causes (n=57)	*P* value
Age, years	74.9 ± 15.2	66.5 ± 13.6	69.8 ± 14.6	0.06
Female gender (%)	24 (57.1)	6 (75.0)	31 (54.4)	1.00
BMI* (median)	27.8 ± 6.0 (26.6)	25.1 ± 4.5 (24.9)	26.7 ± 6.7 (25.4)	0.39
Severe infection (%)**	14 (33.3)	3 (37.5)	26 (45.6)	0.46
Atrial fibrillation (%)	20 (47.6)	2 (25.0)	13 (22.8)	0.03
Diuretic use (%)	35 (83.3)	6 (75.0)	18 (31.6)	< 0.0001
Creatinine, mg/dl (median)	1.8 ± 0.9 (1.7)	1.4 ± 0.9 (1.4)	1.2 ± 1.2 (0.9)	< 0.0001
BNP: PF, pg/ml (median)	1063.2 ± 986.9 (728.8)	366.8 ± 433.7 (204.8)	208.3 ± 214.6 (130.0)	< 0.0001
BNP: blood; pg/ml (median)	1519.2 ± 1121.6 (1325.6)	854.3 ± 870.7 (502.3)	314.1 ± 470.2 (129.8)	< 0.0001
PF/serum protein ratio (median)	0.38 ± 0.14 (0.39)	0.4 ± 0.2 (0.3)	0.6 ± 0.1 (0.7)	< 0.0001
PF/serum LDH ratio (median)	0.47 ± 0.26 (0.41)	0.4 ± 0.1 (0.4)	4.9 ± 17.0 (1.2)	< 0.0001

*BMI was missing in 13 patients (3 in CHF group, 2 in other causes of transudate group, and 8 in non-cardiac causes group)

**Severe infection during the admission period

BMI = body mass index, BNP = B-type natriuretic peptide(pg/ml), CHF = congestive heart failure, LDH = lactate dehydrogenase, PF = pleural fluid

the curve (AUC) of 0.89, 95% confidence interval (95%CI) 0.89–0.95. We could not determine an optimal cutoff point of pleural fluid BNP level for predicting CHF. Suggested cutoff points from our findings ranged from 273.4 pg/ml (sensitivity 83.3%, specificity 72.3%, accuracy 76.7%) to 400 pg/ml (sensitivity 78.6%, specificity 86.2%, accuracy 83.0%).

For 76 patients, we had both pleural fluid BNP and blood BNP measurements. In this group of patients, 39 exhibited exudate and 36 showed transudate according to Light's criteria. In one case, no protein or LDH pleural fluid was measured. These 76 patients were categorized according to blood BNP level: less than 100 pg/ml, 100 pg/ml ≤ BNP ≤ 400 pg/ml, and more than 400 pg/ml. This classification is acceptable in the workup of acute dyspnea. In the group of blood BNP < 100 pg/ml, 78.6% of patients also had low pleural fluid BNP levels. None of these patients had the final diagnosis of CHF. In the group of blood BNP between 100 and 400 pg/ml, 77.8% of patients also had pleural fluid BNP at the same level, but no good correlation was found regarding CHF diagnosis. In the group of blood BNP > 400 pg/ml, only 77.3% of patients had pleural fluid BNP above this value, and the pleural fluid BNP level correlated well (88.2%) with CHF diagnosis [Table 2]. Five patients with CHF had blood BNP levels in the range of 100–400 pg/ml, and the pleural fluid BNP levels were also at the same range.

Eleven patients had CHF with exudative pleural effusion. As a part of this study, we placed emphasis on these patients to determine whether pleural fluid BNP levels can help differentiate the etiology for it. Seven patients had pleural fluid BNP > 400 pg/ml, and four had pleural fluid BNP level from 100 to 400 pg/ml. None of these patients had blood BNP level < 100 pg/ml. We found a good correlation between blood and pleural fluid BNP levels [Table 3].

Table 2. Characteristics of pleural fluid and the correlation to blood BNP levels

	Transudate (n=36)					Exudate (n=39)					Correlation (%)	
			Pleural fluid BNP, pg/ml					Pleural fluid BNP, pg/ml				
Blood BNP (pg/ml)	A	B	‹ 100	100–400	› 400	A	B	‹ 100	100–400	› 400	C*	D**
‹ 100 (n=14***)	0	1	1	0	0	0	12	10	2	0	78.6	100
100–400 (n=18)	4	5	1	8	0	1	8	3	6	0	77.8	35.7
› 400 (n=44)	24	2	0	2	24	9	9	1	7	10	77.3	88.2

A = CHF, B = no CHF

*Correlation between blood BNP and pleural fluid BNP (%)

**Correlation between pleural fluid BNP and diagnosis of CHF (%)

***One patient had no definition of pleural fluid according to Light's criteria

BNP = B-type natriuretic peptide (pg/ml), CHF = congestive heart failure

Table 3. Comparison of blood BNP and pleural fluid BNP levels in patients with exudative pleural effusion and CHF

Patient number	Age, years	Blood BNP, pg/ml	Pleural fluid BNP, pg/ml	Pleural fluid/ blood protein	Pleural fluid/ blood LDH	Reduced LVEF*
1	87	2287.3	844.8	0.51	0.75	Yes
2	79	2555.0	513.6	0.54	0.62	Yes
3	71	457.7	190.5	0.49	0.70	Yes
4	89	377.3	207.7	0.51	1.75	Yes
5	87	1516.3	721.0	0.62	0.72	Yes
6	95	473.3	247.0	0.53	0.61	No
7	79	576.5	506.0	0.68	0.56	Yes
8	47	2918.4	1008.7	0.44	0.97	Yes
9	58	612.3	485.0	0.53	0.50	Yes
10	89	1495.2	849.4	0.57	0.53	Yes
11	87	NA	147.5	0.54	0.76	NA**

*Reduced LVEF by echocardiography

**The diagnosis of CHF was a clinical one

BNP = B-type natriuretic peptide(pg/ml), CHF = congestive heart failure, LDH = lactate dehydrogenase, LVEF = left ventricular ejection fraction, NA = not applicable

DISCUSSION

Blood BNP levels are a useful parameter in the assessment of acute dyspnea [3,4,13]. Pleural fluid BNP levels were suggested as a useful parameter in the assessment of pleural effusion. The accepted cutoff for blood BNP suggesting CHF is 400 pg/ml, while levels below 100 pg/ml exclude this diagnosis. With regard to pleural fluid BNP levels, the cutoff is relatively vague, and NT-proBNP was found to be a better diagnostic tool for establishing the etiology of pleural effusion [7-10].

In this study, we assessed the pleural fluid BNP level as an additional parameter in the workup of patients presenting with pleural effusion. The cutoff that we found was 273.4 pg/ml, although the confidence interval was quite broad (0.015–0.361). In addition, we found good correlation between blood BNP and pleural fluid BNP levels, thus raising doubt in the need to measure pleural fluid BNP in addition to blood BNP levels.

There are only a few studies that have assessed pleural fluid BNP levels. Recent meta-analysis about this topic concluded that more studies need to be conducted to assess the diagnostic accuracy of pleural fluid BNP level. Blood and pleural fluid NT-proBNP are much more accurate as a diagnostic tool for CHF [11].

The main limitation of our study is its relatively small size, as can be seen by the relatively large confidence interval. In addition, we had only 76 patients with both blood and pleural fluid BNP measurements. We found that the blood BNP levels at the non-cardiac group were high as well (314.1 pg/ml), although the range of results was broad, as reflected by the large standard deviation. For example, two patients in this group had a very high blood BNP levels (> 1900 pg/ml) that influenced the average. We could not find the reason for the high blood BNP levels, but CHF was excluded in these two patients. Another factor that impacts on the accuracy of pleural BNP and blood BNP measurement relates to severe infection. It was previously shown that among critically ill patients, non-CHF effusions may exhibit high pleural NT-proBNP [14]. In our study, 40.2%

of the patients were also diagnosed with severe infection during the admission period, but no difference was seen between groups. The high percentage of patients with severe infection might also influence the high blood and pleural BNP levels that were measured in the non-cardiac group.

CONCLUSIONS

High levels of blood BNP in patients presenting with pleural effusion are suggestive of CHF, even when the pleural fluid is exudate. High levels of pleural fluid BNP can support the diagnosis, but have no additional diagnostic value.

Correspondence
Dr. R. Zalts
Dept. of Internal Medicine C, Rambam Health Care Campus, Haifa 3109601, Israel
Phone: (972-4) 777-3309.
Fax: (972-4) 777-2260
email: r_zalts@rambam.health.gov.il

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Capsule

Early detection of ovarian cancer

Ovarian cancer is the fifth leading cause of cancer-related death among females in the United States, owing in part to the late stage at which it is often diagnosed. Survival rates increase dramatically when it is detected early, and new methods for advanced detection are greatly needed. **Williams** and co-authors developed a carbon nanotube-based sensor that optically detects the U.S. Food and Drug Administration-approved high-grade serous ovarian carcinoma (HGSC) CA-125 (cancer antigen 125) and HE4 (human epididymis protein 4) biomarkers. When implanted into live cancer-bearing mice, distinct wavelength responses from individual nanotubes in the device rapidly and repeatedly differentiated mice with ovarian cancer from controls. The same was true in tests using samples from ovarian cancer patients.

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Eitan Israeli

Capsule

Taking CRISPR technology further

CRISPR techniques are allowing the development of technologies for nucleic acid detection. Taking advantages of the distinctive enzymatic properties of CRISPR enzymes, **Gootenberg** and colleagues developed an improved nucleic acid detection technology for multiplexed quantitative and highly sensitive detection, combined with lateral flow for visual readout. **Myhrvold** and co-authors added a sample preparation protocol to create a field-deployable viral diagnostic platform for rapid detection of specific strains of pathogens in clinical samples. Cas12a (also known as Cpf1), a type V CRISPR protein, cleaves double-stranded DNA and has been adapted for genome editing. **Chen** et al. discovered that Cas12a also processes single-stranded DNA threading activity. A technology platform based on this activity detected human papillomavirus in patient samples with high sensitivity.

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