EDITORIAL

PLEURAL EFFUSIONS: THE SEPARATION OF TRANSUDATES AND EXUDATES

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Traditionally, pleural effusions have been separated into transudative and exudative pleural effusions.[1] Transudative effusions occur when the systemic factors influencing the formation and absorption of pleural fluid are altered such that pleural fluid accumulates. Most transudative pleural effusions are due to left ventricular failure or cirrhosis. In contrast exudative effusions occur when the local factors influencing the formation and absorption of pleural fluid are altered such that pleural fluid accumulates. The most common causes of exudative pleural effusions are malignancy, parapneumonic effusions and empyema, tuberculosis and pulmonary embolus. The primary reason to separate transudative from exudative pleural effusions is that if a patient has a transudative pleural effusion, no investigations need be directed toward the pleural and the systemic condition can be treated with the expectation that the effusion will resolve. In contrast, if the patient has an exudative pleural effusion it is important to determine the local disease that is responsible for the effusion. According, additional laboratory tests and at time invasive tests are indicated to demonstrate the etiology of the pleural effusion.

It has been 35 years since I wrote the paper describing Light's criteria for separating transudative from exudative pleural effusions.[2] Light's criteria state that a pleural effusion is an exudate if one or more of the following criteria are met:[1] The ratio of the pleural fluid to the serum protein exceeds 0.50;[2] the ratio of the pleural fluid lactic acid dehydrogenase (LDH) to the serum LDH exceeds 0.6 or[3] the absolute value of the pleural fluid exceeds two thirds the upper normal limit for serum. The thought for using the two different measurements is that the protein reflects the permeability of the vessels where the fluid was formed while the LDH reflects the level of inflammation in the pleural space.

Since the publication of Light's criteria, several other tests have been proposed for the separation of transudates from exudates. Proposed tests have included a pleural fluid cholesterol greater than 60 mg/dL,[3,4] a pleural fluid cholesterol greater than 45 mg/dL,[5] a gradient of less than 1.2 g/dL for the difference between the pleural fluid and serum albumin level, a pleural fluid to serum bilirubin ratio above 0.6,[6] a high pleural fluid viscosity,[7] a high level of oxidative stress markers,[8] soluble

leukocyte selectin,[9] various cytokines,[10] uric acid[11] and a pleural fluid to serum cholinesterase ratio above 0.23.[12]

Subsequent reports comparing the efficacy of Light's criteria with other proposed tests have concluded that Light's criteria best separate exudates from transudates. Romero and coworkers[13] concluded that Light's criteria were superior to cholesterol measurements in a series of 297 patients including 44 transudates and 253 exudates. Burgess and coworkers[14] concluded that Light's criteria were superior to the serum effusion albumin gradient, the effusion cholesterol concentration, and the pleura fluid to serum bilirubin level. Two additional studies[15,16] have made similar conclusions.

The primary problem with Light's criteria is that it misidentifies about 20% of transudates as exudates. This is particularly frequent in patients with heart failure who have been on diuretics. In such instances the transudative criteria of Light are only slightly exceeded, i.e., the protein ratio is between 0.5 and 0.6, or the LDH ratio is between 0.6 and 1.0 or the absolute value of the pleural fluid LDH is between two thirds and equal to the upper limit of normal.

The challenge is to identify the transudates that meet exudative criteria. Burgess and coworkers[14] demonstrated about 12 years ago that most effusions that should be transudative but were classified as exudative had serum-pleural fluid albumin gradients above 1.2 g/dL. Romero et al[17] then demonstrated in 2001 that a serum-pleural fluid protein gradient was just as accurate as the albumin gradient in identifying these effusions. Since the protein gradient is readily available when Light's criteria are determined, it is the recommended test.

Another possible way to identify transudates due to heart failure that meet exudative criteria is to measure the level of N-Terminal-Brain Natriuretic Peptide (NT-pro-BNP) in the pleural fluid. Elevated levels of NT-pro-BNP in the pleural fluid indicate that the pleural effusion is due to congestive heart failure (CHF). When the ventricles are subjected to increased pressure or volume, BNP and the larger amino terminal part NT-pro-BNP of its precursor are released in equimolar amounts into the circulation.[18] The serum levels of BNP are used to help establish the diagnosis of CHF and levels above 500 pg/ml are considered diagnostic of CHF while levels below 100 pg/ml are thought to make the diagnosis of CHF unlikely.[19]

Porcel and coworkers[20] first demonstrated that the pleural fluid levels of NT-pro-BNP are elevated in patients with heart failure. They measured NT-pro-BNP levels in 117 pleural fluid samples with the following diagnoses: CHF-44, malignancy-25, tuberculous pleuritis-20, hepatic hydrothorax-10 and miscellaneous-18. The mean NT-pro-BNP fluid levels in the CHF patients (6931 pg/ml) was significantly higher than that of 551 pg/ml in the patients with hepatic hydrothorax and that of 292 pg/ml in the patients with exudative pleural effusions.[20] When a cutoff level of 1500 pg/ml was used, the sensitivity was 91% and the specificity was 93% for the diagnosis of CHF. We have recently compared the pleural fluid NT-pro-BNP levels in 10 patients each with effusions due to CHF, pulmonary embolism, post coronary artery bypass surgery and malignancy.[21] All the patients with CHF had NT-pro-BNP levels above 1500 pg/ml while none of the other patients had BNP levels this high.[21]

Other workers have also demonstrated the utility of measuring the pleural fluid NT-pro-BNP for diagnosing pleural effusions due to CHF. Tomcsany1 et al[22] measured the pleural fluid and serum NT-pro-BNP levels in 14 patients with congestive heart failure and 14 patients with pleural effusions of other etiologies. In this study the median NT-pro-BNP levels in the patients with CHF and other diseases were 6295 pg/ml and 276 pg/ml in the pleural fluid and 5713 pg/ml and 231 pg/ml in the serum respectively.[22] In this small study the correlation between the pleural fluid and serum NT-pro-BNP levels was very high (R2 = 0.95). In a recent study Kolditz et al.[48] measured

the serum and pleural fluid NT-pro-BNP levels in 93 patients including 25 with CHF. They confirmed the results of the study by Tomcsanyi[22] and coworkers in that the levels of serum and pleural fluid BNP again were closely correlated (R2 = 0.90). They reported that an NT-pro-BNP cutoff level of 4000 pg/ml had a sensitivity of 92% and a specificity of 93% of making the diagnosis of CHF. Moreover, in this study nine patients with heart failure met Light's exudative criteria and all of them had pleural and serum NT-pro-BNP levels greater than 4000 pg/ml.[22] From the latter two studies it appears that there is no need to measure the pleural fluid pro-BNP levels.

It should be emphasized that the BNP measurement used in most laboratories at the present time is the BNP rather than the NT-pro-BNP. In general the levels of BNP tend to be significantly lower (one quarter to one half) than the levels of NT-pro-BNP.[23,24] To my knowledge there is only one paper evaluating BNP as opposed to NT-pro-BNP in patients with pleural effusions and only the BNP level in the serum was measured. In this study[25] a plasma BNP level of 520 had a sensitivity of 97% and a specificity of 89% in identifying CHF as the etiology of the pleural effusion.

In the above discussion pleural effusions have been dichotomized into transudates or exudates based on a single cut-off point. An alternative approach is to use likelihood ratios for identifying whether a pleural fluid is a transudate or an exudates.[34,35] The idea behind this approach is that the higher a value, e.g., the pleural fluid LDH, the more likely the effusion is to be an exudate and the lower the value, the less likely the effusion is to be an exudate. Heffner and his coworkers have derived multilevel[26] and continuous[27] likelihood rations for the usual biochemical tests used to differentiate transudates and exudates. When these likelihood ratios are used in conjunction with pretest probabilities using Bayes' theorem, post-test probabilities can be derived.[27] Difficulties in using this approach occur because the pretest probabilities vary significantly from physician to physician and most physicians do not understand the mathematics involved. This approach does emphasize that it is important to take into consideration the absolute value of the measurements. Very high or very low values are almost always indicative of exudates and transudates, respectively, whereas values near the cut-off levels can be associated with either transudates or exudates.

In conclusion, I recommend the following approach for determining whether a pleural effusion is a transudate or an exudate. First assess Light's criteria. The higher the value for the protein ratio, the LDH ratio and the absolute value of the LDH, the more likely the fluid is an exudate. If the fluid meets the criteria for a transudative effusion, it is a transudate. If the fluid meets the criteria for an exudative effusion by only a small margin and the clinical picture is compatible with a transudative effusion, measure the protein gradient between the serum and pleural fluid. If this value is >3.1 gm/dl, then the fluid can be relabeled a transudate. An alternative approach is to measure the NT-pro-BNP or the BNP in the pleural fluid or the serum. If the level of NT-pro-BNP is greater than 2000 pg/ml and the level of BNP is greater than 520 pg/ml, the diagnosis of congestive heart failure is established.

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