Increased Oxidative Stress in Exudative Pleural Effusions*

A New Marker for the Differentiation Between Exudates and Transudates?

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Study objectives: **Oxidative stress has been associated with various respiratory disorders. We tested the hypothesis that exudates would present higher levels of oxidative stress compared to transudates, expressing the increased local oxidative burst in the former.**
Design: **Prospective, cross-sectional study.**
Patients or participants: **One hundred six consecutive patients who had undergone thoracentesis were studied. Ninety patients with a final diagnosis of pleural effusion were further analyzed.**
Setting: **The respiratory department and a clinical laboratory of a tertiary hospital.**
Interventions: **Subjects underwent diagnostic thoracentesis, and standard biochemical parameters (*ie*, total protein, lactate dehydrogenase, and albumin levels) were measured in pleural fluid and serum. Oxidative stress levels were assessed with a commercially available method (d-ROMs test; Diacron; Grosseto, Italy) that uses conventional Carratelli units (UCarr). In 14 patients, duplicate measurements of oxidative stress and a second thoracentesis were performed on the following day for the assessment of the repeatability of measurements. Receiver operating characteristic (ROC) analysis was performed in order to determine the optimal cutoff level for the differentiation between exudates and transudates.**
Measurements and results: **Oxidative stress levels were higher in exudates compared to transudates (mean [± SD] stress level, 274 ± 72 vs 126 ± 34 UCarr, respectively; $p < 0.0001$). No significant differences were found among the levels of oxidative stress in exudative effusions of different etiologies. The area under the ROC curve was 0.992 (95% confidence interval, 0.945 to 0.997), and the method provided high sensitivity (96.8%), high specificity (96.3%), and high accuracy (96.7%) for the diagnosis of exudates at a cutoff level for oxidative stress of 186 UCarr. Consecutive measurements of oxidative stress in the same samples and on fluid from two different thoracenteses performed on 2 consecutive days presented excellent repeatability.**
Conclusions: **Oxidative stress levels are higher in exudative pleural effusions compared to transudative effusions, probably due to reactive oxygen species produced in the former.**
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Key words: exudates; hydroperoxides; oxidative stress; pleural effusion; transudates

Abbreviations: CHF = congestive heart failure; FN = false-negative; FP = false-positive; LCa = pleural effusions due to lung cancer; LDH = lactate dehydrogenase; OCa = other malignant pleural effusions; ROC = receiver operating characteristic; TB = tuberculosis; TN = true-negative; TP = true-positive; UCarr = Carratelli units

The lung represents unique tissue in both its exposure to higher oxygen tensions and its high concentration of antioxidants.[1] The imbalance between oxidants and antioxidants is referred to as *oxidative stress* and has been associated with various respiratory disorders. Increased oxidative stress participates in the pathogenesis of both airways and parenchymal lung diseases. Asthma, COPD, and bronchiectasis have been associated with inflammation and increased levels of oxidative stress.[2–4] Inflammatory cells generate free radicals in patients with interstitial lung diseases such as pulmonary fibrosis and sarcoidosis.[5,6] Increased oxidant burden has also been found in patients with pleural effusions due to lung cancer (LCa)[7] and obstructive sleep

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apnea.[8] Furthermore, free radicals are closely associated with diseases such as cystic fibrosis, primary pulmonary hypertension, and bronchopulmonary dysplasia.[9–11]

Various markers of oxidative stress, including hydrogen peroxide and 8-isoprostane, have been reported to be increased in the lung. Such markers have been determined in various biological samples, as in blood,[12,13] sputum,[14] BAL fluid,[15] and exhaled breath condensate[16,17] collected from patients with lung diseases. These samples express either local or systemic levels of oxidative stress. The pleural cavity is a closed space that is segregated from the rest of the respiratory system but interacts with the lung in different disease processes. However, the local production of free radicals and the role of oxidative stress in the pathogenesis of pleural effusions have not been extensively studied.

Pleural effusions are often a diagnostic dilemma for the physician as the differential diagnosis is wide. The first step in the evaluation of pleural effusions is the distinction between exudates and transudates. The criteria described by Light et al[18] have become a standard method for this separation because of their high sensitivity in identifying exudates. The main disadvantage appears to be the misclassification of transudates as exudates.[19] More recent studies have proposed other methods for the differentiation of exudates and transudates.[20–22]

The aim of the present study was to evaluate the levels of oxidative stress in the pleural fluid of patients with pleural effusions of various etiologies. We tested the hypothesis that exudates would present higher levels of oxidative stress compared to transudates, expressing the increased local oxidative burst in the former. We also examined whether oxidative stress could serve as an independent marker for the differentiation between exudative and transudative pleural effusions. Finally, we validated the method we used for the assessment of oxidative stress by testing the repeatability of the measurements on the same samples and on samples taken from the same subjects on 2 consecutive days.

Materials and Methods

Subjects

This study was performed on patients who were hospitalized in the Respiratory Medicine Department of the Medical School of the University of Thessaly in Larissa between May and December 2004. During this time, 106 consecutive patients who had undergone diagnostic thoracentesis for pleural effusions were studied. Sixteen of these patients were excluded from this study if either, despite extensive evaluation, the cause of the pleural effusion was indeterminate, or more than one plausible cause of the pleural effusions was present. The study protocol was approved by the local ethics committee, and all subjects gave their written informed consent.

Sample Collection and Analysis

Pleural fluid and blood samples were collected from all patients on the day of their hospital admission. All samples were immediately analyzed using standard commercially available methods for the following biochemical parameters: glucose; total protein lactate dehydrogenase (LDH); and albumin. Aliquots of the pleural fluid samples were additionally used for the determination of the levels of oxidative stress.

Diagnostic Criteria for Pleural Effusions

The determination of the etiology of the pleural effusions was based on the clinical presentation, the results of appropriate diagnostic tests, and the response to treatment for each patient. Accordingly, effusions were classified into the following groups, which were defined by predetermined criteria:

1. Effusions secondary to LCa were diagnosed by the demonstration of malignant cells on cytologic examination or in a biopsy specimen or histologically proven primary lung malignancy with the exclusion of any other cause of pleural effusion.
2. The diagnosis of tuberculous effusions was based either on the presence of positive stain or culture for *Mycobacterium tuberculosis* (TB) in the pleural fluid, sputum, or pleural biopsy specimen; or in the presence of typical caseating granulomas on a pleural biopsy specimen. When a pleural biopsy was not performed, we considered patients to have tuberculous pleurisy if they met the following criteria: (1) adenosine deaminase levels in pleural fluid of > 40 U/L[23]; (2) the exclusion of any other cause of pleural effusion; and (3) the response to antituberculous therapy.
3. Other malignant pleural effusions (OCas) were clearly secondary to ovarian malignancy, breast malignancy, renal cell carcinoma, and non-Hodgkin lymphoma in patients in whom other causes for the development of pleural effusions had been excluded.
4. Infectious (parapneumonic) effusions were identified by the presence of pulmonary infections associated with acute febrile illness, pulmonary infiltrates, purulent sputum, and the response to antibiotic treatment; identification of the organism in the pleural fluid; or the presence of empyema, which was associated with a finding of franc pus in the pleural cavity. None of these patients presented any radiologic signs of loculation at the time of the thoracentesis.
5. Other exudates included effusions that were attributed to rheumatoid arthritis, eosinophilic pleural effusions, and posttraumatic effusions.
6. The diagnosis of congestive heart failure (CHF) was based on the findings of an enlarged heart and/or pulmonary venous congestion on a chest radiograph, evidence of left ventricular systolic or diastolic dysfunction on echocardiography, peripheral edema, and/or response to treatment for CHF.
7. Renal failure was diagnosed by increased levels of urea and creatinine in the presence of fluid overload and by the exclusion of other causes for the development of pleural effusions.
8. Other causes of transudative pleural effusions included the following: nephrotic syndrome diagnosed in patients with proteinuria, edema, and hypoalbuminemia; liver cirrhosis diagnosed by liver biopsy in the presence of ascites; and

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