A simple laboratory measurement for discrimination of transudative and exudative pleural effusion: Pleural viscosity

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Plasma viscosity; Pleural viscosity; Pleural effusion; Transudate; Exudate

Summary
Background: The initial step in establishing the cause of an effusion is to determine whether the fluid is a transudate or exudate. Plasma viscosity is influenced by the concentration of plasma proteins and lipoproteins with the major contribution resulting from fibrinogen. In this study we aimed to evaluate the role of pleural fluid viscosity in discrimination of transudate and exudates.

Materials and Methods: We studied prospectively 63 consecutive patients with pleural effusion in whom diagnostic or therapeutic thoracentesis had been performed. The criteria of Light were applied to differentiate transudates from exudates: 33 patients (23 male, 13 female, mean age = 68 ± 4 years) had exudates and 30 patients (17 male, 13 female, mean age = 68 ± 5) had transudates (due to congestive heart failure). Measurements of pleural fluid and plasma viscosity were performed using a viscometer.

Results: There was no statistically significant difference between patients with transudate and exudates in respect to plasma viscosity. However, pleural viscosities of the patients with exudates were significantly higher than those of patients with transudate (1.37 ± 0.16 mPa vs 0.93 ± 0.03 mPa, p < 0.001, respectively). Pleural viscosity has a high sensitivity, specificity (94%, 93%, respectively), positive and negative predictive value (97%, 97%, respectively) for the discrimination of transudative or exudative pleural fluid.

Conclusion: We have demonstrated for the first time that pleural viscosity of the exudative effusion is higher than that of transudative effusion with high sensitivity,
Introduction

The development of inflammation in the pleura results in an increased vascular permeability leading to pleural fluid accumulation. This pleural fluid is enriched in proteins, inflammatory cells, and mediators.\(^1\)\(^,\)\(^2\) Classification of pleural effusions into transudates and exudates is based on pleural fluid absolute lactic dehydrogenase value, fluid to serum ratio of and fluid to serum ratio of total protein used in a parallel combination strategy. Since additional diagnostic or therapeutic interventions will be tailored based on the transudative or exudative nature of the pleural fluid, it is a crucial diagnostic step to categorize the effusion as an exudates or transudate.\(^3\) Multiple investigations have examined the discriminative properties of different pleural fluid tests for identifying exudative effusions.\(^4\)\(^,\)\(^5\) Established clinical practice has favored diagnostic strategies that combine pleural fluid lactate dehydrogenase, the ratio of pleural fluid to serum lactate dehydrogenase, and the ratio of pleural fluid to serum protein combined in “or” rules (Light’s criteria)\(^4\) wherein an exudative effusion is identified if any one of the criteria is fulfilled.

Plasma viscosity is influenced by the concentration of plasma proteins and lipoproteins with the major contribution resulting from fibrinogen.\(^6\) The physico-chemical or rheological approach states that the contribution of individual plasma proteins and lipoproteins to plasma viscosity depends on their concentration, molecular weight, rigidity and asymmetrical shape.\(^7\)\(^,\)\(^8\) It has been previously reported that plasma viscosity has a valuable importance and can be used as an acute phase reactant.\(^9\) In this study we aimed to evaluate the role of pleural fluid viscosity in discrimination of transudate and exudates.

Materials and methods

We studied prospectively 63 consecutive patients with pleural effusion in whom diagnostic or therapeutic thoracentesis had been performed. The criteria of Light et al.\(^4\) were applied to differentiate transudates from exudates: 33 patients (23 male, 13 female, mean age = 68 ± 4 years) had exudates and 30 patients (17 male, 13 female, mean age = 68 ± 5) had transudates (due to congestive heart failure). Exudative pleural effusions meet at least one of Light criteria (namely, pleural fluid/serum protein ratio, pleural fluid/serum LDH ratio, pleural fluid LDH concentration). If none of these criteria is met, the patient has transudative pleural effusion. Eighteen exudates were considered malignant (three patients with small extensive stage cell lung cancer, 15 patients with stage IV non-small lung cancer), since malignant cells were detected on cytologic examination of the pleural fluid or biopsy specimens. A pleural effusion was considered parapneumonic (\(n = 12\)) when there was an acute febrile illness, with purulent sputum and pulmonary infiltrates, in the absence of malignancy or other diseases causing exudate and neutrophilia in pleural fluid. Tuberculous pleural effusion was diagnosed in two patients by positive culture findings for *Mycobacterium tuberculosis* or a pleural biopsy specimen showing typical epithelioid cell granulomas. After the first successful thoracentesis of pleural fluid, a specimen was subjected to routine biochemical analysis including tests for total protein, glucose, and lactate dehydrogenase. A second sample was added to a tube containing ethylenediaminetetra-acid–potassium anticoagulant for differential cell counting. Bacterial cultures and cytologic examinations were performed on all pleural effusions. Measurements of pleural fluid and plasma viscosity were performed using Brookfield DV-II viscometer. One milliliter of plasma was separated by centrifugation at 3000 rpm for 10 min and used for plasma viscosity measurement. Viscosity was measured in a Brook–field DV-Iviscometer (Brookfield, Stoughton, MA) at shear rates of 100, 20, and 5 s\(^{-1}\) at 37 °C. Hospital ethic committee approved the study protocol and all patients gave informed consent.

Statistical analysis

Continuous variables are presented as mean ± s.d., and categorical variables are presented as percentage. Unpaired t-test was used to compare continuous variables between two groups. McNemar test was used to compare categorical variables in
dependent groups. ROC analysis was also performed to find a cutoff point for differentiating exudates and transudate. Sensitivity and specificity of pleural viscosity were calculated by normal procedure. A p-value less than 0.05 was considered as statistically significant. Receiver operator characteristic (ROC) analysis was carried out to determine sensitivity, specificity, positive predictive value and negative predictive value in relation to a number of cutoff values of pleural viscosity for discrimination of exudate and transudate. P-values below 0.05 were defined as statistically significant.

Results

Plasma levels of albumin, and protein in patients with transudate did not differ statistically from those in patients with exudates (P > 0.05, Table 1). However, plasma levels of lactate dehydrogenase tended to be higher in patients with exudates (P = 0.055). Pleural fluid albumin, protein and lactate dehydrogenase were found to be higher in patients with exudates than in those with transudate as expected (P < 0.001, Table 1). There was no statistically significant difference between patients with transudate and exudates in respect to plasma viscosity. However, pleural viscosity of the patients with exudates was significantly higher than that of patients with transudate (1.37 ± 0.16 mPa vs 0.93 ± 0.03 mPa.s P < 0.001, respectively, Table 1, Fig. 1). The sensitivity, specificity, and predictive values of pleural viscosity for the discrimination of exudate or transudate in pleural effusion were determined by ROC analysis. The area under the ROC curve and the values for sensitivity and specificity, as well as the positive and negative predictive values for defined pleural viscosity cut-off levels are displayed in Table 2. Regarding the cutoff value of 1 mPa.s, pleural viscosity has a high sensitivity, specificity (94%, 93%, respectively), positive and negative predictive value (97%, 97%, respectively) for the discrimination of transudative or exudatetive pleural fluid. Sensitivity, specificity, positive and negative predictive value of pleural protein/plasma protein ratio, pleural lactate dehydrogenase/plasma lactate dehydrogenase for discrimination of transudate from exudates according to Lights’ criteria were also calculated separately and compared to plasma viscosity (Table 3). Positive predictive value (97%) and specificity (93%) of the plasma viscosity were found to be significantly higher than those of pleural protein/plasma protein criteria (70%, 60%, respectively, P = 0.01).

Discussion

There are many causes of pleural effusion, and correct diagnosis remains a major challenge to clinicians. The initial step in establishing the cause of an effusion is to determine whether the fluid is a transudate or exudate. An exudative pleural effusion results from disease of the pleural surface, while a transudative effusion results from an imbalance of Starling’s forces resulting in movement of fluid into the pleural space. Pleural fluid formed through a normal capillary membrane is a transudate that is characterized by little protein or other large molecules. An exudate refers to pleural fluid that is formed through abnormally permeable capillary walls and contains higher concentration of protein than do transudates. Established clinical

Table 1 Characteristics of transudative and exudative pleural fluids.

<table>
<thead>
<tr>
<th></th>
<th>Transudate</th>
<th>Exudate</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma albumin</td>
<td>3.16 ± 0.5</td>
<td>3.07 ± 0.18</td>
<td>0.29</td>
</tr>
<tr>
<td>Plasma protein</td>
<td>6.56 ± 0.58</td>
<td>6.66 ± 0.60</td>
<td>0.50</td>
</tr>
<tr>
<td>Plasma LDH</td>
<td>627 ± 112</td>
<td>677 ± 83</td>
<td>0.055</td>
</tr>
<tr>
<td>Pleural albumin</td>
<td>1.17 ± 0.17</td>
<td>1.65 ± 0.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural protein</td>
<td>2.66 ± 0.5</td>
<td>3.09 ± 0.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural LDH</td>
<td>267 ± 52</td>
<td>566 ± 160</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Plasma viscosity</td>
<td>1.45 ± 0.06*</td>
<td>1.46 ± 0.05#</td>
<td>0.51</td>
</tr>
<tr>
<td>Pleural viscosity</td>
<td>0.93 ± 0.03</td>
<td>1.37 ± 0.16</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* vs pleural viscosity P < 0.001, # vs pleural viscosity P = 0.002.
practice has favored diagnostic strategies that combine pleural fluid lactate dehydrogenase, the ratio of pleural fluid to serum lactate dehydrogenase, and the ratio of pleural fluid to serum protein combined in "or" rules (Light’s criteria), wherein an exudative effusion is identified if any one of the criteria is fulfilled. More recent studies have examined the diagnostic utility of pleural fluid cholesterol, bilirubin, and albumin concentrations comparing the sensitivities and specificities of the new tests with the three-test combination of Light’s criteria. Pleural fluid C reactive protein has also been shown to be helpful in distinguishing exudative from transudative pleural fluid. Increased pleural levels of vascular endothelial growth factor and matrix metalloproteinases is associated with exudative pleural effusion suggesting increased vascular permeability and inflammation-mediated fluid accumulation.

The development of inflammation in the pleura results in an increased vascular permeability leading to pleural fluid accumulation. This pleural fluid is enriched in proteins, inflammatory cells, and mediators. The management of pleural effusion is still a difficult clinical problem. The fact that plasma viscosity is also influenced by other acute-phase proteins, like α2-macroglobulin, certain immunoglobulins, and large lipoproteins, renders it a biochemically composite variable. Plasma viscosity can be measured quickly, cheaply, and reproducibly. Furthermore, it shows only minimal intraindividual variability.

We have found that pleural viscosity of the patients with transudative pleural effusion is significantly lower than that of patients with exudative pleural effusion and, pleural viscosity is a highly sensitive and specific laboratory measurement in distinguishing exudative and transudative pleural effusion with a cutoff value of 1 mPa.s. Sensitivity, specificity of the pleural viscosity are also comparable to those of pleural LDH to plasma LDH ratio. However, specificity and negative predictive value of pleural protein to plasma protein ratio for the discrimination of transudate and exudates are significantly lower than those of plasma viscosity. Since the exudative pleural effusion is mainly due to alterations in plasma membrane and increased membrane permeability and it contains higher concentration of proteins, it is reasonable to expect high pleural viscosity. However, there is no significant difference between patients having exudative and transudative pleural effusion in respect to plasma viscosity. Regarding the whole circulating plasma volume in the body, it contains lots of macro and micro molecules affecting plasma viscosity. On the other hand, relatively low volume of pleural fluid compared to plasma volume, even small changes or accumulation of macro or micro molecules might change the pleural fluid viscosity where the only important factors are pleural membrane permeability or hydrostatic pressure. Although pleural viscosities are lower compared to plasma viscosity in both patients groups, the pleural viscosity of the patients having transudative effusion is more significantly lower compared to plasma viscosity than those of patients having exudative effusion. This finding indirectly also implies that the main contributing factor for the formation of pleural fluid is the increased hydrostatic pressure rather then the permeability of the pleural membrane in congestive heart failure or transudative fluids.

### Table 2
ROC analysis of pleural viscosity for discrimination of pleural fluid and comparison with.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases</th>
<th>ROC area (95% CI)</th>
<th>Sensitivity/specificity (%)</th>
<th>PPV/NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transudate/Exudate</td>
<td>30/33</td>
<td>0.97 (0.95–1.007)</td>
<td>94%/93%</td>
<td>97%/97%</td>
</tr>
</tbody>
</table>

Pleural viscosity cutoff (pg/ml) <1: transudates, ≥1: exudates, PPV: positive predictive value, NPV: negative predictive value.

### Table 3
Comparison of the sensitivity, specificity, positive and negative predictive values of pleural viscosity, pleural protein/plasma protein, pleural LDH/plasma LDH ratio for discrimination of transudate from exudate.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural viscosity (≥ 1 mPa.s)</td>
<td>94</td>
<td>93</td>
<td>97</td>
<td>97</td>
</tr>
<tr>
<td>Pleural protein/plasma protein (&lt; 0.5)</td>
<td>100</td>
<td>60*</td>
<td>70*</td>
<td>100</td>
</tr>
<tr>
<td>Pleural LDH/plasma LDH (&lt; 0.6)</td>
<td>100</td>
<td>91</td>
<td>91</td>
<td>91</td>
</tr>
</tbody>
</table>

* vs pleural viscosity and pleural LDH/plasma LDH ratio P = 0.01, LDH: lactate dehydrogenase, PPV: positive predictive value, NPV: negative predictive value.
In conclusion, we have demonstrated for the first time that pleural viscosity of the exudative effusion is higher than that of transudative effusion with high sensitivity, specificity, positive and negative predictive value. Regarding the simplicity of this measurement it may play a valuable role in the accurate and fast discrimination of pleural fluid.

References