Role of Biochemical Tests in the Diagnosis of Large Pericardial Effusions*

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**Study objectives:** To determine the biochemical characteristics of large pericardial effusions in various disease states, and to assess their utility as diagnostic tools.

**Setting:** An academic university hospital in the Western Cape, South Africa.

**Design:** Consecutive, prospective case series.

**Patients:** One hundred ten hospital patients > 12 years old, who presented to the echocardiography department with large pericardial effusions, and 12 control subjects who underwent open-heart surgery (coronary artery bypass graft or aortic valve replacement).

**Measurements:** Fluid was sent for examination of biochemistry, adenosine deaminase, microbiology, hematology, and cytology. The etiology of each pericardial fluid sample was established using predetermined criteria.

**Results:** The biochemistry of pericardial exudates differed significantly from pericardial transudates. Light’s criteria (whereby an exudate is defined as having one or more of the following: pleural fluid/serum protein ratio > 0.5; pleural fluid/serum lactate dehydrogenase [LDH] ratio > 0.6; and/or pleural fluid LDH level > 200 U/L) were applied to pericardial fluids and demonstrated to be the most reliable diagnostic tool for identifying pericardial exudates. The corresponding sensitivity was 98%.

**Conclusion:** Although laboratory tests are a useful guideline when assessing the etiology and pathophysiology of pericardial effusions, the majority of large, clinically significant pericardial effusions result from exudative causes.

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**Key words:** exudates; Light’s criteria; pericardial effusions; transudates

**Abbreviations:** ADA = adenosine deaminase; CHF = congestive heart failure; LDH = lactate dehydrogenase; NPV = negative predictive value; Fe/S = pericardial serum ratio; PPV = positive predictive value; P/S = pleural serum ratio; SEAG = serum effusion albumin gradient; ZN = Ziehl-Nielson

Pericardial effusions are present in a variety of pathologic conditions. The advent of echocardiography has provided an accurate noninvasive method for diagnosing the presence of such effusions. However, the etiology of the effusion is often uncertain and cannot always be clearly defined on the basis of clinical assessment or even autopsy. With few validated tests available, investigators have successfully made correct diagnoses on pericardial fluid analysis in 24 to 93% of cases in reported series. Rapid diagnosis and treatment are, however, crucial in reducing morbidity and mortality from pericardial disease.

In contrast to the relatively well-documented ability of tests on pleural fluids to identify the cause of pleural effusions, only one study has reported the systematic evaluation and utility of various diagnostic tests when applied to pericardial fluids. The purpose of this study was to examine the diagnostic utility of several biochemical tests in pericardial fluids.

**Materials and Methods**

A prospective study was carried out from February 1995 to February 1998 at Tygerberg Hospital, South Africa; consecutive patients who presented to the echocardiography department with large pericardial effusions were included in the study. All patients gave written informed consent for participation in the study, which was approved by the Ethics Committee of the University of Stellenbosch. Each patient was subjected to a full clinical
examination, chest radiography, ECG, echocardiography, HIV testing, and sputum Ziehl-Nielson (ZN) staining. A pericardial tap was performed under echocardiographic guidance through a pigtail catheter, and the fluid sent for examination of biochemistry, adenosine deaminase (ADA), microbiology (including ZN staining and culture for Mycobacterium tuberculosis), and hematology. The patient was followed up daily for signs of cardiac tamponade and/or recurrence of effusion.

A total of 110 pericardial effusions were collected during this 3-year period. The hospital records of all patients were reviewed, and a diagnosis was made according to predetermined criteria. Tuberculous pericarditis was diagnosed if one or more of the following criteria was met: (1) identification of the bacillus in pericardial fluid or biopsy specimen by stain and/or by culture, or by the presence of granulomas in pericardial biopsy tissue; (2) positive sputum ZN and/or culture findings in the presence of clinical and radiologic evidence of tuberculosis and in the absence of any other obvious cause associated with pericardial effusions; and (3) clinical and radiologic evidence of tuberculosis in the absence of any other obvious cause associated with pericardial effusions and associated with a positive response to antituberculous therapy. Infective effusions included: (1) pericardial effusions associated with acute febrile illness and responsiveness to antibiotic treatment or identification of the organism in the pericardial fluid; (2) septicemia, characterized by pericardial effusions and multisystem involvement in the presence of positive blood culture findings; and (3) other obvious infective conditions in the absence of any other cause associated with pericardial effusions. Neoplastic effusions were diagnosed when one of the following criteria was met: (1) the presence of cytologic and/or histologic evidence of a malignant pericardial effusion, or (2) histologic proof of a malignant tumor with exclusion of any other cause known to be associated with pericardial effusions. Other effusions were defined by effusions that were clearly caused by collagen vascular disease, congestive heart failure (CHF), uremia, renal failure, and various other rare but well-documented causes of pericardial effusions. Idiopathic effusions were defined as effusions that were not due to any demonstrable cause. A full diagnostic workup had been performed in these patients, and all test results were negative. Patients having multiple superimposed diseases or effusions of unknown origin (that is, all possible etiologic causes could not be excluded) were classified as “indeterminate origin.”

The effusions were classified, according to the etiologic diagnosis, as being transudates or exudates. Only six effusions were included in the transudative group (two patients with CHF and four patients with renal failure). For this reason, 12 control patients were also included in this group for the purpose of this study. Control patients were evaluated by obtaining pericardial fluid during routine open-heart surgery (nine coronary artery bypass procedures and three aortic valve replacements) by open pericardial aspiration. None of these patients had diseases or were receiving medications known to cause pericardial effusions; in addition, none of these patients had experienced myocardial infarctions in the preceding 1 month.

The following parameters were estimated and calculated: (1) the criteria of Light et al.5 (these criteria, initially described in pleural fluids, were modified accordingly for pericardial fluids to include pericardial fluid/serum [Pc/S] protein ratio, Pc/S lactate dehydrogenase [LDH] ratio, and pericardial fluid LDH concentration); (2) total cholesterol; (3) Pc/S cholesterol ratio; (4) serum-effusion albumin gradient (SEAG); and (5) Pc/S bilirubin ratio.

The accuracy of each test in distinguishing between pericardial exudates and transudates was established. In addition, the utility of each biochemical parameter for identifying pericardial effusions was evaluated by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy. Interval (continuous) variables were expressed as mean (SD). Nonparametric data were expressed as median (range). Statistical analysis of continuous variables was performed using the Mann-Whitney U test. A p value < 0.05 was considered statistically significant.

Results

The results from 122 pericardial fluids were analyzed, including 110 due to large pericardial effusions and 12 from control patients. In 10 cases, the pericardial effusion was secondary to multiple (n = 6) or unknown (n = 4) causes; these effusions were excluded. The remaining 112 effusions included 94 exudative effusions and 18 transudative effusions. Exudative effusions included those diagnosed as tuberculous (n = 64), malignant (n = 12), infective (n = 5), and “other” exudates (n = 13), based on the degree of inflammation inherent in each disease process.2,6,7 Transudates included those effusions due to renal failure (n = 4), CHF (n = 2), and normal control subjects (n = 12). There were no significant differences in any biochemical parameters between transudates resulting from CHF or renal failure, and those collected from normal control patients.

Exudative effusions were then compared with transudates. While the RBC counts were similar, exudates had significantly higher fluid leukocyte counts than transudates (median, 2.97 × 10⁹ cells/mL [range, 0.08 × 24.4/10⁹ cells/mL] vs median, 1.15 × 10⁹ cells/mL [range, 0.09 to 4.63 × 10⁹ cells/mL]; p < 0.05). The proportions of neutrophils and monocytes did not differ. A few differences between exudates and transudates occurred among the chemistry tests evaluated, as shown in Table 1. The ability of each test to correctly classify fluid as exudate or transudate was evaluated using the cutoff points generally used for pleural fluids.

Exudate Criteria

According to the criteria of Light et al.5 an exudate is defined as fulfilling one or more of the following: pleural fluid/serum (P/S) protein ratio > 0.5; pleural fluid LDH concentration > 200 U/L; and/or P/S LDH ratio > 0.6. These criteria were applied to pericardial fluids and estimated in 112 patients; 105 of the patients were correctly classified (diagnostic efficiency, 94%). The sensitivity and specificity for an exudate were calculated at 98% and 72%, respectively.

Two of the 94 patients having exudates were misclassified as transudates. These included one patient with an idiopathic pericardial effusion and one patient with systemic sclerosis. Of the transu-
Of the 85 exudates, 60 were correctly classified, while 15 of the 18 transudates were correctly classified. The three transudates that were misclassified were all due to renal failure; only one transudate was correctly classified by the criteria of Light et al.\textsuperscript{5} The PPV and NPV were 95% and 38%, respectively.

Different cutoff levels for cholesterol concentration were applied. The best results were obtained using a cutoff level of 1.15 mmol/L. At this level, sensitivity, specificity, PPV, NPV, and efficiency were 88%, 56%, 90%, 50%, and 83%, respectively. Use of SEAGs did not affect our results.

Pc/S cholesterol ratios were also calculated at various cutoff points. Although Hamm et al\textsuperscript{9} demonstrated that application of a P/S cholesterol ratio did not affect the sensitivity and specificity of this test, this was not the case in our pericardial population. A cutoff ratio of 0.25 yielded an accuracy, sensitivity, and specificity of 87%, 91%, and 67%, respectively; increasing the cutoff ratio to 0.3 yielded results of 88%, 91%, and 83%, respectively.

**Pc/S Bilirubin Ratio**

Meisel et al\textsuperscript{11} described pleural exudates as having a P/S bilirubin ratio $\geq 0.6$. Pc/S bilirubin ratios were calculated in 101 patients with pericardial effusions in the present study. Best results were obtained using a cutoff level of 0.5. Of the 84 exudates, 76 were correctly classified, and 11 of 17 transudates were correctly classified. Efficiency, sensitivity, and specificity for the detection of pericardial exudates were 86%, 90%, and 65%, respectively. The PPV was 93%, and the NPV was 58%.

**Table 1—Summary of the Biochemical Characteristics of Pericardial Exudates and Transudates**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Transudates</th>
<th>Exudates</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pericardial protein, g/L</td>
<td>24.39 (12.67)</td>
<td>55.16 (12.53)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pc/S Protein ratio</td>
<td>0.40 (0.23)</td>
<td>0.79 (0.17)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pericardial LDH, U/L</td>
<td>121.5 (88–811)</td>
<td>798 (82–13005)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pc/S LDH ratio</td>
<td>0.46 (0.32–3.01)</td>
<td>2.62 (0.2–47.27)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pericardial cholesterol, mmol/L</td>
<td>1.22 (0.64)</td>
<td>1.93 (0.68)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pc/S cholesterol ratio</td>
<td>0.25 (0.15)</td>
<td>0.75 (0.50)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pericardial bilirubin, μmol/L</td>
<td>7 (2–34)</td>
<td>20.5 (1–254)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pc/S bilirubin ratio</td>
<td>0.44 (0.13–2.43)</td>
<td>1.80 (0.13–36.3)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pericardial albumin, g/L</td>
<td>11.72 (6.78)</td>
<td>23.92 (7.30)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Serum-pericardial albumin gradient, g/L</td>
<td>21.5 (1–36)</td>
<td>3.5 (9–27)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pericardial ADA, U/L</td>
<td>8.85 (1.5–104)</td>
<td>54.7 (0.8–303.6)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pericardial glucose, mmol/L</td>
<td>4.1 (3.2–9.4)</td>
<td>3.95 (0.04–21)</td>
<td>NS</td>
</tr>
<tr>
<td>Pericardial WBC, 10^6/mL</td>
<td>1.15 (0.09–4.63)</td>
<td>2.97 (0.08–24.4)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Interval (continuous) data are expressed as mean (SD). Ordinal data are expressed as median (range). NS = not significant.
Table 2—Comparison of the Various Biochemical Parameters Used to Differentiate Between Pericardial Exudates and Transudates

<table>
<thead>
<tr>
<th>Methods</th>
<th>Efficiency, %</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light’s criteria*</td>
<td>94</td>
<td>98</td>
<td>72</td>
<td>95</td>
<td>87</td>
</tr>
<tr>
<td>SEAG</td>
<td>90</td>
<td>90</td>
<td>89</td>
<td>98</td>
<td>64</td>
</tr>
<tr>
<td>Cholesterol (1.55 mmol/L)</td>
<td>73</td>
<td>73</td>
<td>83</td>
<td>95</td>
<td>38</td>
</tr>
<tr>
<td>Cholesterol (1.15 mmol/L)</td>
<td>83</td>
<td>88</td>
<td>56</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td>Pc/S cholesterol ratio (0.3)</td>
<td>88</td>
<td>91</td>
<td>83</td>
<td>95</td>
<td>64</td>
</tr>
<tr>
<td>Pc/S bilirubin ratio</td>
<td>86</td>
<td>90</td>
<td>65</td>
<td>93</td>
<td>58</td>
</tr>
</tbody>
</table>

*From Light et al.5

**DISCUSSION**

Very few studies have analyzed the differentiation of pericardial fluids into transudates and exudates. A study by Meyers et al.2 demonstrated that exudates and transudates are best discriminated by specific gravity > 1.015, fluid protein level > 30 g/L, Pc/S protein ratio > 0.5, fluid LDH value > 300 U/L, and Pc/S LDH ratio > 0.6. Another article12 reporting three ill-defined cases with purported transudative pericardial fluid noted specific gravities of 1.018 to 1.022, protein levels of 44 to 50 g/L, and glucose levels of 70 to 90 mg/dL. A further case series noted that inflammatory pericardial fluid had a mean (SD) pH of 7.06 (0.07) compared with noninflammatory fluid, which had a mean ± SD pH of 7.42 ± 0.06.13

From the current study, the criteria of Light et al5 was the most sensitive diagnostic tool (98%) for identifying pericardial exudates. The corresponding specificity was 72%. The major disadvantage appears to be the misclassification of transudates as exudates, especially when the patient is receiving concurrent diuretic therapy. The occurrence of an exudative range of protein levels in patients with CHF receiving diuretic therapy was described in pleural effusions by Pillay14 and Chakko et al.15,16 It is probable that a similar mechanism exists in the case of pericardial effusions.

The SEAG has been used successfully in pleural effusions8 and ascites17–19 to discriminate between exudates and transudates. Application of this concept to pericardial effusions resulted in a sensitivity and specificity of 90% and 89%, respectively, for the identification of pericardial exudates. The major advantage of this biochemical test was the reduction in the number of patients with transudates receiving concurrent diuretic therapy being misclassified as having exudates.

The use of effusion cholesterol levels, Pc/S cholesterol ratios, and Pc/S bilirubin ratios were examined in pericardial effusions. The results were not as reliable as those found using the preceding two methods. The results of these biochemical tests are summarized in Table 2.

In this study population, only 6 of 110 pericardial effusions originated from transudative causes. While this may suggest that the majority of large, clinically significant pericardial effusions are due to exudative causes, it must be emphasized that the incidence of the various types of pericardial effusions seen in this study population differs significantly from first-world countries. Tuberculosis, which accounts for < 4% of all cases in first-world countries,20 was the most prevalent cause in this series, where it accounted for approximately 58% of all pericardial effusions.

Laboratory tests are a useful guideline when assessing the etiology of pericardial effusions. The initial distinction between transudates and exudates gives an indication of the pathophysiological mechanisms, the differential diagnoses, and the need for further investigations. It is important, however, that when making this distinction, these tests are interpreted in conjunction with the physician’s clinical acumen.

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