Applicability of Light's Criteria in the Biochemical Analysis of Pericardial Fluid

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Background --- Biochemical analysis of pericardial effusion is a good diagnostic tool in the management of the probable etiologies of the effusion. Although few validated tests are available, investigators have successfully made correct diagnoses based on pericardial fluid analysis. The application of Light's criteria to classify transudates from exudates of pericardial effusion has been proven to be applicable. This study aimed to evaluate the applicability of Light's criteria in pericardial effusion for cost-effective clinical approach to management of cases in the local setting.

Methods --- This is a validity test utilizing all the pericardial fluids submitted for biochemical study in the laboratory of Philippine Heart Center from January 2002 to June 2008. Receiver Operating Characteristics analysis was used to assess the degree of diagnostic accuracy of the tests using similar parameters used for pleural fluid.

Results --- Most of the pericardial fluid samples were hemorrhagic and a total RBC count cut-off of 100 000 x 10^6/L was used, gathering a sample population of 44 out of 143. All pericardial fluids were misclassified as exudates using the classic Light's criteria. Other biochemical, infectious work-up, cytology and surgical reports, together with the final diagnosis, utilized for the final classification of the fluids revealed 11 transudates and 33 exudates. ROC showed that a pericardial fluid has a higher cut-off value as compared to pleural fluid. The value for fluid LDH was >1000 U/L at 72.7% sensitivity and 78.8% specificity, pericardial fluid/serum LDH was >3.0 at 81.8% sensitivity and 54.5% specificity, and pericardial fluid/serum protein ratio was >0.8 at 45.5% sensitivity and 57.6% specificity but not discriminatory.

Conclusion --- The Light's criteria may be utilized in the initial evaluation of pericardial fluids although higher cut-off values can be employed because of the behavior and characteristic of pericardial fluids as compared to pleural fluids. LDH value of >1000U/L has the best discriminatory power compared to LDH ratio. In this study, the TPAG ratio had the least utility. More study samples including a bigger normal control group are recommended for further confirmation of our current findings.. ***Phil Heart Center J 2012;16:50-54.***

Key Words: Pericardial fluid ■ Light' Criteria ■ Lactate Dehydrogenase ■ total protein

Initial evaluation of pleural effusion is to know whether it is a transudate or an exudate, which can be done using the Light's criteria, although there are instances when this criteria mistakenly classified a transudate as an exudate. The landmark study of Light and coworkers reported that a pleural fluid (PF) to serum protein (P) ratio (R) > 0.5, PF to serum lactate dehydrogenase (LDH) ratio > 0.6, and PF LDH concentration >200 IU/L combined in a parallel "or" rule to identify a fluid as an exudate. The PF LDH criterion was later modified to more than two thirds the upper limit of a laboratory's normal LDH range to account for variations in assay methods.[2] For the past 33 years, this criteria is the most commonly used to separate transudative from exudative pleural effusion. In contrast to well-documented use of these criteria in pleural effusions, fewer studies have been done to evaluate the application of Light's criteria in pericardial effusions.

Accumulation of fluid in the pericardial cavity (pericardial effusion) is most frequently caused by damage to the lining of the cavity associated with changes in the permeability of the membranes due to infection (pericarditis), malignancy, or metabolic damage (uremia).[3] Exudates include cases of malignancy and infection like tuberculosis while transudates are secondary to congestive heart failure, post-operative syndrome

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uremia and SLE. The biochemical analysis of pericardial effusion is a good diagnostic tool in the appropriate management of the most probable etiologies of the effusion. Combination of different tests tended to perform better and demonstrated higher sensitivities and odds ratios compared with individual tests.

Although few validated tests are available, investigators have successfully made correct diagnoses based on pericardial fluid analysis in 24 to 93% of cases in reported series.[3,4] In the study of Meyers et.al.[5] , they concluded that the evaluation of pericardial fluid could be limited to cell count, glucose, protein and lactate dehydrogenase determinations plus bacteriologic culture. Other tests that may be highly specific for a particular disease should be ordered based on a high index of suspicion. Follow up study done by Burgess[6] et.al., showed that laboratory tests are useful guidelines when assessing the etiology and pathophysiology of pericardial effusions. They concluded that majority of large pericardial effusions are exudates while in the study of Meyers,[5] neither the volume nor the appearance of the pericardial fluid differed between exudates and transudates. These studies both used Light's criteria to distinguish transudates from exudates and concluded that it is indeed applicable in pericardial effusions.

No local study has been done yet to apply the Light's criteria in pericardial effusion, which may prove useful in clinical management of the patient. This study aimed to evaluate the applicability of Light's criteria in pericardial effusion for cost-effective clinical approach to management of cases of pericardial effusion in the local setting. Specifically, the study aims to determine the validity of each component of the Light's criteria in classifying pericardial effusion, to determine the classification of pericardial effusions based on Light's criteria and to propose a cut-off value applicable for pericardial fluids for test components in Light's criteria based on other available biochemical tests, cell count cytology and final diagnosis as additional tools in classifying pericardial effusions.

METHODOLOGY

This is a validity study conducted at the Philippine Heart Center, Biological and Clinical Laboratory Division, from January 2002 to June 2008. Included were pericardial fluids of patients with pericardial submission, wherein the following tests were conduected: pericardial LDH and TPAG with serum LDH and TPAG; with additional cell differential count; additional GS/CS, KOH, AFB stain, cytology and surgical report. Excluded were samples of pericardial fluid classified as traumatic tap (RBC count of more than 100,000x10^6) and inavailability of medical chart for review.

Sample size and basis for calculation. Sample size was computed based on a 20% rate of transudate from the study of Porcel et al.[7]. Using a relative error of 20% and $\alpha = 0.05$, the computed sample size was 163.

All pericardial fluids submitted for analysis in the laboratory from January 2002 to June 2008 were included. Serum and pericardial fluid protein and pericardial fluid and serum LDH were measured using VITROS Chemistry System 950 (Ortho-Clinical Diagnostics, Johnson & Johnson Company, USA). Previous pericardial fluid LDH and protein with available serum LDH and protein in the Laboratory Information System (Labtrak) were added to the sample population. Additional biochemical tests available were obtained in the Labtrak including cell count, fluid GS/CS, KOH, AFB, blood CS, cytology and surgical reports and medical records of the patients were reviewed to obtain the final diagnosis as the reference standard for the final classification of the fluid.

Using cut-off values of the pleural fluid Light's criteria, the pericardial fluids were classified as transudate or exudate with at least 2 of the 3 criteria namely, a) Fluid LDH more than 2/3 of the upper limit of the serum LDH (2/3 of 618 U/L), b) Fluid to serum ratio of LDH >0.6, and c) Fluid to serum TPAG >0.5. The results of other tests (microbial stains, culture, cytology and pertinent surgical reports) were tabulated and analyzed to aid in the final diagnosis which served as reference standard to render the fluids as true transudates and true exudates.

Statistical Analysis. The sensitivity and specificity of the Light's criteria were determined. Subsequent receiver operating characteristics (ROC)[8] analyses were determined to identify the most discriminating cut-off values for fluid LDH, LDH ratio and TPAG ratio.

RESULTS

The total sample population collected from January 2002 to June 2008 was 143 patients, short of 20 samples from the target sample size of 163 (87%). The pericardial fluid cell counts revealed total white cell counts ranging from 4 to 170 000 x 10^6/L, and total red cell counts ranging from 50 to 4330000 x 10^6/L. Eighty nine (89) patients were with available medical charts for review. With the large number of hemorrhagic samples due to possible contamination with peripheral blood, the authors opted to use a cut-off red cell count of 100,000 x 10^6/L. The final sample population was reduced to 44 patients.

Twenty six males and eighteen females comprised the sample population (see Table 1). Ages ranged from few months old to seventy nine years old.

Using the Light's criteria, all the fluids were classified as exudates (see Table 2). Using the reference standard, (composite tests analysis with final clinical diagnosis), 11 of the 44 samples were classified as transudates with a computed sensitivity of 75% and specificity of zero for the Light's criteria.

Table 3 shows the mean values for the true transudates and true exudates with elevated mean values for fluid LDH, LDH ratio and protein ratio and wide standard deviations. The p values were insignificant.

Receiver operating characteristic curves (Figures 1, 2, and 3), were computed for each parameter, fluid LDH, ratio of fluid/serum LDH and ratio of fluid/ serum protein. ROC curves showed that the most likely cut-off value for fluid LDH was 1000 mmol/L, with sensitivity and specificity of 72.7% and 78.8%, respectively. The PPV and NPV were 53.3% and 89.7%, respectively. The cut-off ratio of LDH was >3.0, with sensitivity and specificity of 81.8% and 54.5%, respectively. The PPV and NPV were 37.5% and 90.0%, respectively. Likewise, the ratio of protein was >0.8 with sensitivity and specificity of 45.5% and 51.6%, respectively. The PPV and NPV were 26.3% and 76%, respectively.

Table 1. Demographic profile of patients with pericardial effusion (PHC, 2009)

Characteristics	Frequency (%) or range n=44
Age Range (y.o)	0.36-79
Gender	
Male	26 (59)
Female	18 (41)

Table 2. Sensitivity and Specificity of Light's Criteria in the Classification of Pericardial Fluids. (PHC, 2009)

Classification using Light's Criteria	Classification based on Reference Standard*		
	Transudate	Exudate	Total
Transudate	0	0	0
Exudate	11	33	44
	Sn = 75%	Sp = 0%	

* See text for explanation

Table 3. Mean values es of Biochemical Parameters Used to Classify Transudates and Exudates of the Pericardial Fluid Included in the Study (PHC, 2009)

Variables	Transudate (n = 11) Mean ± SD	Exudate (n = 33) Mean ± SD	P-value
PF LDH	2967.00 ± 6536.6	6674.2 ± 8197.3	O.181 NS
Ratio LDH	2.30 ± 3.39	8.41 ± 10.41	O.064 NS
Ratio TPAG	0.799 ± 0.045	0.813 ± 0.252	O.868 NS

DISCUSSION

With very limited studies available on the nature of pericardial fluids, there is no strong evidence if pericardial fluid characteristics are like its counterpart, pleural fluid. Whether the parameters used for pleural fluid biochemical properties are applicable to pericardial fluid, remain uncertain and the evidence is elusive. Although there are studies supporting that pericardial effusions could be treated like pleural fluids, e.g. using Light's criteria for classification of transudates and exudates[5,6], there are few new

studies that have proven it otherwise [9,10]. In a study of Ben Horin (2005), 30 samples obtained from open-heart surgery showed that the physiological composition of the pericardial fluid has relatively higher value as compared to pleural fluid.[10] The fluid LDH level was unexpectedly high, averaging 2.4 times the serum level, and the mean protein level was 0.6 of the serum. Of these 30 pericardial fluids examined, 28 met pleural fluid biochemical criteria for exudates, and only 2 fulfilled the "transudative" conventions. Thus, the study concluded that the Light's Criteria were not probably applicable to classify the type of pericardial effusion. The inherent high LDH level was also supported by another study (Ben Horin et.al, 2007) of 59 patients undergoing elective open-heart surgery in whom the average fluid:serum LDH ratio was >1.6 and the average fluid: serum protein ratio was >0.5. This study did not claim the usefulness of these parameters for classification of pericardial effusions.

Our findings were comparable to the two latter studies mentioned in which our transudative fluid LDH, LDH ratio and protein ratio were relatively high. Our study showed the pericardial fluid LDH had a mean of 4.8x than upper level of serum, mean LDH ratio 2.3 and mean protein ratio 0.7. With the reference standards derived from the final clinical diagnosis and other laboratory tests available, the final classification of the fluids showed that it followed the 20 per cent occurrence of transudates, similar to that of pleural fluids. With these findings, the validity of adopting the classic Light's criteria for the evaluation of pathologic pericardial effusions is debatable.

One of the proposed reasons for high LDH levels in pericardial fluid is its location. The more likely increased fluid LDH is due to probable preferential leak from the adjacent perimyocardial tissue.[9,10] The increased protein ratio may be more difficult to explain. In our institution, patients are referred due to congestive heart failure with impending cardiac tamponade. Most of them are from other institutions and are sent for further management. Usually, they are initially treated to stabilize the congestion and were given diuretics. In a study of Chakko et. al[11], he mentioned that there is increased protein gradient and ratio in patients treated with diuretics. This may also apply to pericardial effusion particularly in our samples, since similar biochemical properties like pleural fluid are observed.

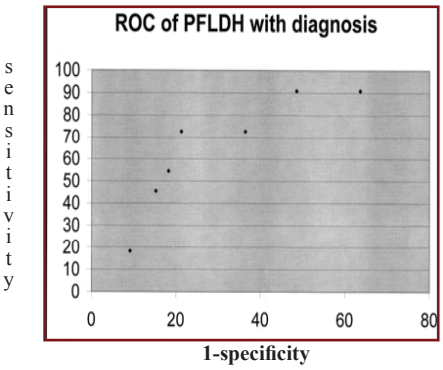
Since samples with peripheral blood contamination were excluded in our analysis, these samples' characteristics were also described. Eleven (11) per cent of these fluids were transudates based on the reference standard. Thus, using a cut-off of 100 000x10^6/L red blood cells does not create a significant bias against hemorrhagic fluids. The computed fluid fluid LDH and fluid to serum LDH ratio cut-offs by ROC were attained and may prove clinically useful.

CONCLUSION

Pericardial fluids behave differently from their pleural fluid counterpart. The utilization of Light's criteria to classify the fluid as transudate or exudate should be used with caution. The pericardial fluid transudates have relatively high LDH levels averaging 4.8x the upper level of serum, mean LDH ratio of 2.3x and mean protein ratio of 0.7x. Our findings show that higher cut-off values may be used to correctly classify the fluids. Fluid LDH of >1000 U/L, LDH ratio of >3.0 and protein ratio of >0.8 are the cut-off values for exudates. Of the 3 test components of the proposed modification of the Light's criteria, the fluid LDH level has the highest discriminatory power.

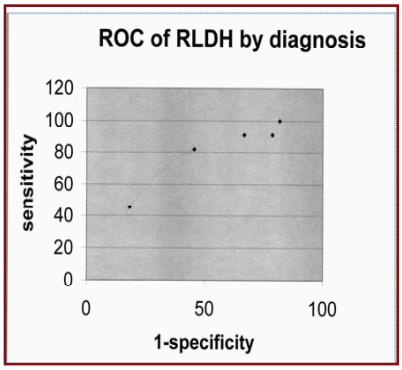
LIMITATION OF THE STUDY AND RECOMMENDATION

The study has a limited sample population. Further collection of data, both normal and abnormal pericardial fluids is recommended to strengthen the statistics of the investigation. All the fluids received should have a pericardial fluid panel of tests, e.g. serum LDH and TPG, fluid LDH and TPG, fluid cell count, infectious work-up, cytology and histopathology examination for good reference standards. These should be counter-checked with the final diagnosis of the patients. Other confounding effects of diuretics should be noted. The method of collection should be noted to properly screen hemorrhagic tap. Furthermore, pericardial fluid normal values from open heart surgery patients will be the best control samples for comparison and further description of fluid characteristics.



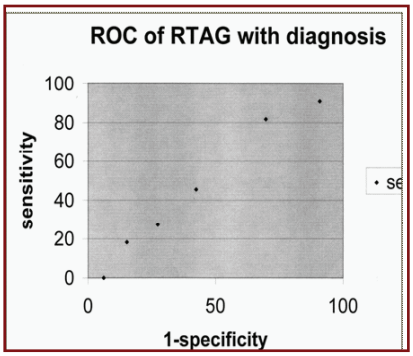
Cut-off value - 1000IU/L
Sensitivity - 72.7 Specificity - 78.8
PPV - 53.3 NPV - 89.7

Figure 1. Receiver operating characteristcs (ROC) of pericardial fluid in LDH. (PHC, 2009)



Cut-off value - >3.0
Sensitivity - 81.8 Specificity - 54.5
PPV - 37.5 NPV - 90.0

Figure 2. Receiver operating characteristcs (ROC) of pericardial fluid to Serum LDH. (PHC, 2009)



Cut-off value - >0.8
Sensitivity - 45.5 Specificity - 57.6
PPV - 26.3 NPV - 76.0

Figure 3. Receiver operating characteristcs (ROC) of pericardial fluid to Serum TPAG (PHC, 2009)

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