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Role of Pleural Fluid Cholesterol in Pleural Effusion

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Additional information is available at the end of the chapter

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Abstract

Pleural effusion occurs when formation and accumulation of pleural fluid exceeds its absorption. It indicates an imbalance between pleural fluid formation and its removal. Pleural fluid accumulates in settings of increased hydrostatic pressure, increased vascular permeability, decreased oncotic pressure, increased intrapleural negative pressure and decreased lymphatic drainage. On the basis of pathophysiology, pleural effusion can be transudates or exudates. It is important to establish an accurate etiological diagnosis so that the patient may be treated in a rational manner. Using Light's criteria may need other extra investigations to differentiate transudates and exudates but using pleural fluid cholesterol (pCHOL) will help to diagnose them with only the pleural fluid analysis. Moreover the albumin or protein gradient will need serum as well as the pleural fluid investigations and will have more financial burden than just investigating pleural fluid cholesterol. Pleural cholesterol is thought to be derived from degenerating cells and vascular leakage from increased permeability. Thus pleural fluid cholesterol is one of the important investigations that can distinguish exudates from transudates. Routine use of pleural fluid cholesterol for classifying pleural effusion should be encouraged to improve the accuracy, sensitivity and specificity.

Keywords: pleural effusion (PE), pleural fluid cholesterol (pCHOL), transudates, exudates, pleural fluid lactate dehydrogenase (pLDH), serum lactate dehydrogenase (sLDH), congestive heart failure (CHF)

1. Introduction

Pleurae are the continuous membranes of the serous pleural sac that invest and enclose the lungs. They are called parietal and visceral pleura. The visceral pleura is also called the pulmonary pleura that closely covers the lung and is adherent to its surfaces. The parietal pleura adhere to the diaphragm, mediastinum and the wall of the thorax. It consists of costal

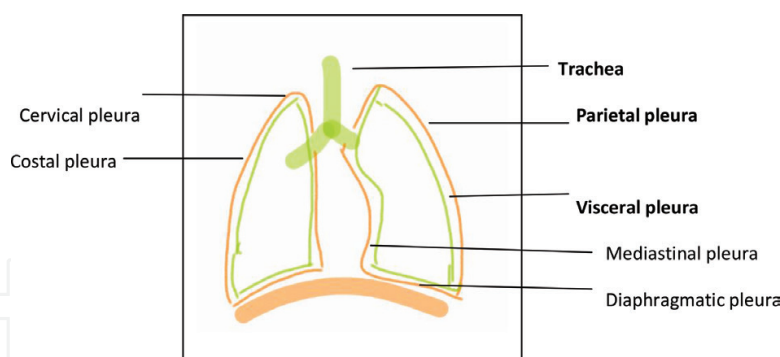


Figure 1. Schematic diagram of pleura and pleural cavity.

pleura, mediastinal pleura, diaphragmatic pleura and cervical pleura. The pleural space lies between the lung and the chest wall and is bounded by the parietal and visceral membranes. It contains a thin layer of fluid that serves as a coupling system called pleural fluid. A pleural effusion (PE) is present when there is an excess fluid in the pleural space. It indicates an imbalance between pleural fluid formation and its removal. It is important to establish an accurate etiological diagnosis so that the patient may be treated in a rational manner.

The pleural space is a real, not potential, space that is approximately 10–20 μm wide and extends completely around the lung to the hilar root [1, 2]. When air or fluid collects between the two layers, the pleural cavity expands. The schematic diagram for pleural cavity and pleurae is in **Figure 1**.

Pleural fluid is formed from the systemic vessels of the pleural membranes at an approximate rate of 0.6 ml/h and is absorbed at a similar rate by the parietal pleural lymphatic system. Normally, the pleural spaces contain approximately 0.25 ml/kg of low protein liquid. Disturbances in either formation or absorption result in the accumulation of excess pleural fluid [3].

The volume of pleural fluid is small, approximately 0.1–0.2 ml/kg in different studies. From parietal pleural capillaries, there is constant movement of fluid into the pleural space at a rate of 0.01 ml/kg bodyweight/h. There is a balance of the formation (entry) and absorption (exit) of the pleural fluid. The resultant homeostasis leaves 5–15 ml of fluid in the normal pleural space [4]. For pleural effusion to be there must be an increase in entry rate or a reduction in exit rate.

The parietal pleura has a hydrostatic pressure similar to that of the systemic circulation (30 cm H_2O), whereas that of the visceral pleura depends on the pulmonary circulation (10 cm H_2O). Oncotic pressure is similar in both (25 cm H_2O), but the pressure within the pleural cavity is affected by the gravity gradient. Thus, the pleural space is heterogeneous with a nondependent portion in which Starling forces favor outpouring of fluid into the cavity and the parenchymal capillaries [5].

2. Pathophysiology

The mechanism of pleural liquid formation is that the liquid originates from the systemic vessels of the pleural membranes, not from the pulmonary vessels [6]. It means that pleural

liquid is interstitial fluid of the systemic pleural microvessels. There are three major considerations that support this hypothesis [7]:

- i. The systemic vessels (of both parietal and visceral pleural membranes) are adjacent to the pleural space and are much closer to the pleural space than are the pulmonary vessels.
- ii. The low pleural liquid protein concentration (1 g/dl) and ratio to the plasma protein concentration (0.15 g/dl) are consistent with a filtrate from high-pressure systemic vessels. Large particles will be sieved and relatively restrained compared to the liquid if liquid and protein are filtered at high-pressure and high flow across a semi permeable membrane. Thus, plasma proteins, being large, will be retarded much more than the liquid in their movement across a membrane, and the protein concentration of the resultant filtrate will be low. On the other hand, if liquid and protein are filtered at low pressure and low flow, proteins are retarded less, and the protein concentration of the resultant filtrate is higher. Filtrates from low-pressure pulmonary vessels, e.g., lung lymph, have a high protein concentration (4.5 g/dl) and ratio (0.7) compared to filtrates from systemic vessels and to pleural liquid. Of note in this argument, pleural liquid formation is described as high flow, whereas its measured rate is relatively slow (0.01 ml/kg/h). However, it is the filtration at the systemic microvessels that is described as high as or at least higher than filtration across pulmonary microvessels. Some of that filtrate is reabsorbed into the low-pressure post capillary venules, and some is removed by bulk flow via the local lymphatic vessels. It is only the remainder that then moves into the low-pressure pleural space.
- iii. In situations where systemic pressure varies, the pleural liquid protein concentration varies in concert. For example, systemic hypertensive rats have a lower pleural liquid protein-to-plasma protein concentration ratio than do normotensive rats (0.42 versus 0.55), even though their pulmonary pressures are the same [8]. During development from the fetus to the adult, systemic blood pressure generally rises and pulmonary pressure falls. In a study in sheep, the pleural protein ratio decreased with development, as would be expected if the pleural liquid originated from the high-pressure systemic vessels [9].

2.1. Increased fluid entry

Excess liquid filters out of microvessels based on a balance of hydrostatic and osmotic forces across a semi permeable membrane [1, 6]. These forces are well described in the Starling equation, in which the hydrostatic forces that filter water out of the vessel are balanced by osmotic forces that reabsorb water back into the vessel [10, 11].

$$\text{Flow} = k \times [(P_{mv} - P_{pmv}) - s (\pi_{mv} - \pi_{pmv})]. \quad (1)$$

In this equation, k is liquid conductance of the microvascular barrier, P_{mv} and P_{pmv} represent hydrostatic pressure in the microvascular and perimicrovascular compartments, respectively, s is the reflection coefficient for total protein and ranges from 0 (completely permeable) to 1 (completely impermeable), and π_{mv} and π_{pmv} represent protein osmotic pressure in microvascular and perimicrovascular liquids, respectively and s is Staverman's reflection coefficient. In normal micro vessels, there is ongoing filtration of a small amount of low protein liquid. The flow can increase with changes in various parameters of the Starling equation.

Increase in permeability: An increase in flow can be due to increases in either liquid conductance (an increase in k) or protein permeability (a decrease in reflection coefficient). If the endothelial barrier becomes more permeable to liquid and protein, for example, there will be an increase in flow of a higher protein liquid. Because absorption does not alter the protein concentration of pleural liquid, pleural liquid with a high protein concentration indicates its origin from a circulation across an area of increased permeability.

Increase in microvascular pressure: An elevation in venous outflow pressure induces the elevation of microvascular pressure (P_{mv}). Increases in arterial pressure are less likely to be transmitted to the microvessels because of the high precapillary resistance and autoregulation of arteriolar tone.

Elevations in either systemic venous pressure (affecting the parietal pleura) or pulmonary venous pressure (affecting the visceral pleura) can lead to an increase in pleural liquid formation and the development of a pleural effusion. As vascular permeability is unchanged in this setting, the increased flow is associated with a greater sieving of proteins, leading to a filtrate with a lower protein concentration than normal (with a pleural liquid-to-plasma protein ratio of less than 0.15). Of course, most effusions formed due to increased microvascular pressures, i.e., transudative effusions, have a pleural liquid-to-plasma protein ratio much higher than this, between 0.4 and 0.5. This fact demonstrates that most liquid must arise from a source other than the systemic circulation of the pleural membranes. The likely source is the large non-systemic circulation adjacent to the pleural space, namely the pulmonary circulation of the nearby lung. In the normal state, lung interstitial liquid, e.g., lymph, filtered from the low-pressure pulmonary circulation has a protein concentration ratio [12] (lung to plasma protein concentration ratio) of 0.7, but with increased flow due to increased pulmonary microvascular pressures, this ratio falls to 0.4–0.5. This lung interstitial oedema liquid then is the likely source of the majority of the hydrostatic pleural effusion [13].

The way lung liquid reach the pleural space is that when the rate of filtrate formation exceeds the absorptive capacity of the lung lymphatics, the filtrate accumulates in the peribronchovascular spaces (“cuffs”) [14]. Once in these interstitial spaces, the liquid is not accessible to lung lymphatics [15].

Thus, although the lymphatics are undeniably important in removing liquid as it is filtered from the pulmonary circulation, they cannot account for the clearance of already established oedema from the lung [16]. This interstitial oedema probably leaves the lung by flowing down pressure gradients along the interstitial spaces (interlobular septae, peribronchovascular bundles and visceral pleura) of the lung toward either the mediastinum or the pleural space. The entry of large amounts of lung interstitial liquid into the pleural space will elevate the overall protein concentration of the pleural liquid, giving a ratio of 0.40–0.50, the expected range for a transudative effusion [16].

Decrease in pleural pressure: A decrease in pleural pressure, as seen with significant atelectasis, may alter the balance of forces described in the Starling equation by reducing the pressures surrounding the nearby micro vessels. This decrease in perimicrovascular pressures

(Ppmv) can enhance filtration across the microvascular barrier of a low protein liquid (with a pleural liquid-to-plasma protein ratio of less than 0.15).

Decrease in plasma osmotic pressure: Hypoproteinemia (due to hypoalbuminemia) will decrease the plasma oncotic pressure (π_{mv}), thereby increasing the forces favoring filtration until the balance is restored. By itself, hypoproteinemia can probably induce small effusions with a low protein concentration. In addition, hypoproteinemia can lower the threshold for effusion formation when other Starling forces are changed. In a study of hospitalized patients with AIDS, for example, hypoproteinemia alone was the apparent cause of 19% of all pleural effusions [17]. Together with other factors, a lower plasma protein concentration may have contributed to effusion formation in many more patients, because, in general, all patients with effusions had a lower plasma albumin concentration than those without effusion (2.5 versus 3.4 g/dl).

2.2. Decreased fluid exit

A decrease in exit rate reflects a reduction in lymphatic function. Because lymphatic function is poorly understood, much of this discussion is speculative. Unlike blood vessels, lymphatic vessels have one-way valves and propel lymph using both their own rhythmic contractions and the respiratory motions of the chest wall. In addition, flow is affected by lymphatic patency, availability of liquid, and the pressures influencing filling (pleural pressure) and emptying (systemic venous pressure) of lymphatics [18–20].

Intrinsic factors: A number of factors can interfere with or inhibit the ability of lymphatic's to contract, including:

- Cytokines and products of inflammation (e.g., endotoxins)
- Endocrine abnormalities (e.g., hypothyroidism)
- Injury due to radiation or drugs (e.g., chemotherapeutic agents)
- Infiltration of lymphatics by cancer
- Anatomic abnormalities (e.g., yellow nail syndrome)

Extrinsic factors: Multiple extrinsic factors can inhibit lymphatic function although the lymphatics themselves are normal. These include:

- Limitation of respiratory motion (e.g., diaphragm paralysis, lung collapse and pneumothorax)
- Extrinsic compression of lymphatics (e.g., pleural fibrosis and pleural granulomas)
- Blockage of lymphatic stomata (e.g., fibrin deposition on pleural surface and pleural malignancy)
- Decreased intrapleural pressure (e.g., trapped lung caused by a fibrous rind on the visceral pleura)

Normal pleural fluid resembles water in appearance and clarity, and is odorless [20]. Its chemical composition is summarized in **Table 1**.

Pleural effusion is present when there is excess accumulation of pleural fluid due to its exceeding formation on pleural fluid absorption. At normal circumstances, pleural fluid entering the pleural space from the capillaries in the parietal pleura is removed by the lymphatics which can absorb 20 times more fluid than is formed.

Fluid can enter the pleural space from the interstitial spaces in the visceral pleura or through the diaphragmatic pores from the peritoneal cavity. So pleural effusion will develop in two circumstances:

1. When there is excess formation of pleural fluid from parietal pleura, interstitial spaces from the lung and peritoneal cavity.
2. When there is inability of removal of pleural fluid by the lymphatics.

Local factors: There is change in the pleural surface permeability due to which the exudative pleural effusion occurs.

Systemic factors: There is increase in pulmonary capillary wedge pressure (PCWP) or decrease in oncotic pressure that result in alteration of formation and absorption of pleural fluid as in transudative pleural effusion.

Translocation of fluid: Small pores in diaphragm act as pathways for peritoneal fluid to enter into the pleural cavity as in hepatic hydrothorax. It may be massive even without marked ascites.

Parameters	Value
Volume	0.1-0.2ml/kg
Cells	1000-5000/mm3
Mesothelial cells	3- 70%
Monocytes	30-75%
lymphocytes	2-30%
Granulocytes	10%
Protein	1-2gm/dl
Albumin /protein	50-70%
Glucose	as in plasma
Lactate Dehydrogenase	< 50% of plasma

Table 1. Normal composition of pleural fluid.

The basis in which accumulation of pleural fluid occurs are: increased hydrostatic pressure, increased vascular permeability, decreased oncotic pressure, increased intrapleural negative pressure and decreased lymphatic drainage.

Pleural effusion may be of two types depending upon the underlying pathology, i.e., transudative and exudative. The causes of transudative and exudative pleural effusion are summarized in **Tables 2** and **3**, respectively.

Transudate will be clear fluid with low protein while exudates will have cloudy fluid with high protein. Exudates have a ratio of protein in pleural fluid and serum >0.5 ; ratio of LDH in pleural fluid and serum >0.6 and pleural fluid LDH $> 2/3$ rd of upper limit of serum LDH. Protein in transudate is less than 2.5 g/dl while exudates have higher values [21].

Transudative pleural effusion is usually due to the increased hydrostatic pressure that is caused by congestion in the capillaries, e.g., in heart failure and there is formation of pleural fluid from the increased venous pressure of the pleural membranes. However in case of exudates, there is vascular leakage of fluid due to increased permeability as a result of inflammation.

1.	Increased hydrostatic pressure	Congestive Heart Failure Superior vena cava syndrome Pericardial effusion Constrictive cardiomyopathy Massive pulmonary embolism
2.	Decreased capillary Oncotic pressure	Cirrhosis of Liver Nephrotic syndrome Malnutrition Protein losing enteropathy Small Bowel disease
3.	Transmission from Peritoneum	Any cause of ascites Peritoneal Dialysis
4.	Increased capillary permeability	Small pulmonary emboli Myxoedema
5.	Miscellaneous	Urinothorax Acute atelectasis Wet Beriberi Idiopathic

Table 2. Transudative pleural effusion.

1. Respiratory causes	Parapneumonic effusion Tuberculosis sarcoidosis Parasitic infections Pulmonary embolism Trapped lung
2. Gastrointestinal causes	Pancreatitis Postoperative Intrabdominal abscesses Posttransplant of liver Esophageal perforation Endoscopic variceal sclerotherapy
3. Cardiac causes	Post Myocardial Infarction Constrictive pericarditis PostPericardiotomy
4. Occupational	Asbestosis
5. Traumatic	Hemothorax
6. Post surgical	Coronary artery bypass surgery
7. Autoimmune causes	Systemic lupus erythematosus Rhematoid pleurisy Drug induced lupus Sjogren syndrome Wegener's granulomatosis Chrug strauss Syndrome
8. Endocrine causes	Hypothyroidism Ovarian hyperstimulation syndrome
9. Renal related	Uremia Peritoneal dialysis
10. Malignancies and complications	Mesothelioma Metastases Superior vena caval obstruction
11. Drug induced	Bromocriptine,Dantrolene, Nitrofurantoin, Amiodarone,etc
12. Lymphatic cause	Chylothorax

13. MISCELLANEOUS	Amyloidosis
	Iatrogenic injury
	Radiation therapy
	Yellow nail syndrome

Table 3. Exudative pleural effusion.

3. Clinical features

The clinical features of pleural effusion depend on the amount, the rate of accumulation of fluid and the underlying cause. In acute cases, the symptoms appear suddenly. Patients may present with shortness of breath, pleuritic pain, cough and constitutional symptoms. Dyspnea may result from compression of lung tissue and from mechanical alterations in the respiratory muscles as the fluid changes their length-tension relationship. There will be associated symptoms related to the etiology of the pleural effusion. So careful elicitation of history in cases of pleural effusion may streamline the physician toward the etiological aspect of pleural effusion.

Physical examination reveals decreased respiratory movements on the affected side and displacement of mediastinum to the opposite side. If there is an associated collapse of lung or fibrosis, the trachea may be central or may even be pulled to the same side depending on the degree of collapse or fibrosis. Tactile fremitus may be decreased to absent but may also be increased toward the top of large effusion. Percussion reveals dull to flat note over the fluid.

Auscultation reveals decreased to absent breath sounds but bronchial breath sounds may be heard near top of large effusion. Pleural rub can also be heard and sometimes crackles above the level of effusion. Frequently, there are E to A changes (egobronchophony) at the upper fluid border where underlying lung parenchyma is compressed.

4. Diagnostic clues for exudates from transudates

Light et al. in 1972 found a criteria to have sensitivity and specificity of 99% and 98%, respectively, for differentiating transudative and exudative PE (ratio of protein in pleural fluid and serum >0.5 ; ratio of LDH in pleural fluid and serum >0.6 and pleural fluid LDH $> 2/3$ rd of upper limit of serum LDH) [21]. But the other investigators could only reproduce specificities of 70–86% using light's criteria. Also it is found that 25% of patients with transudates pleural effusion are mistakenly identified as having exudative effusion by Light's criteria.

Most transudates have absolute total protein concentrations below 3.0 g/dl (30 g/l), although acute diuresis in heart failure can elevate protein levels into the exudative range [22–24].

If one or more of the exudative criteria are met and the patient is clinically thought to have a condition producing a transudative effusion, the difference between the protein levels in

the serum and the pleural fluid should be measured. If this gradient is >31 g/l (3.1 g/dl), the exudative categorization by these criteria can be ignored because almost all such patients have a transudative pleural effusion [25]. About only 75% of cases, the etiology of pleural effusion can be established with the clinical presentation, biochemical parameters and fluid cytology. Despite extensive diagnostic work up in about 20% of pleural effusion, the etiology remains unknown [26].

From meta-analysis, Heffner et al. has identified pleural effusion of exudative type with at least one of the following condition [27]:

- Pleural fluid protein >2.9 g/dl
- Pleural fluid cholesterol >45 mg/dl (1.16 mmol/l)
- Pleural fluid LDH $> 2/3$ rd of upper limit of serum

Roth et al. [28] found that despite the high sensitivity of Light's criteria (100%), these criteria had a low specificity (72%). Using an albumin gradient of 1.2 g/dl or less to indicate exudates and greater than 1.2 g/dl to indicate transudates, 57 of the 59 patients (41 exudates; 18 transudates) were correctly classified. Two patients with malignant effusions were misclassified as having transudates.

In 2003 National medical journal of India, one article published by Guleria R of AIIMS, New Delhi [29] found that for exudative pleural effusion, pleural fluid cholesterol ≥ 60 mg/dl has 92% accuracy, 88% sensitivity and 100% specificity; however, Light's criteria was 98% sensitive and 80% specific.

Evaluation through pleural fluid cholesterol only can avoid the financial burden and double pricks (serum and pleural fluid) in anxious patients to go through the series of tests to confirm the exudative pleural effusion.

In a study done in Nepal by Hamal et al. [30], pleural fluid cholesterol (pCHOL) is highly correlated than protein ratio (pleural fluid protein/serum protein) with clinical diagnosis for exudates. It is found that in transudates, parapneumonic, tubercular and neoplastic pleural effusion, pCHOL levels were 0.53 ± 0.28 , 1.81 ± 0.59 , 2.08 ± 0.58 and 1.58 ± 0.65 mmol/l, respectively. With a classifying threshold of 1.16 mmol/L, pCHOL has a sensitivity of 97.7% and specificity of 100% for diagnosis of exudates with accuracy of 98.3%.

Pleural cholesterol is thought to be derived from degenerating cells and vascular leakage from increased permeability. Though the cause of the rise in cholesterol levels in pleural exudates is unknown, two possible explanations have been put forward.

According to the first, the cholesterol is synthesized by pleural cells themselves for their own needs [31] (extrahepatic synthesis of cholesterol is now known to be much greater than was once thought, depends on the metabolic needs of cells, and is in dynamic equilibrium with cholesterol supply by LDL and cholesterol removal by HDL) [32] and the concentration of cholesterol in pleural cavity is increased by the degeneration of leukocytes and erythrocytes, which contain large quantities.

The second possible explanation is that pleural cholesterol derives from plasma; some 70% of plasma cholesterol is bound to low density, high molecular weight lipoproteins (LDL) and the rest to HDL or very low density lipoproteins (VLDL) and the increased permeability of pleural capillaries in pleural exudate patients would allow plasma cholesterol to enter the pleural cavity.

The cause of the increased cholesterol concentration is unknown, but two hypotheses are available [33, 34]: (A) cholesterol production by different cells has been recognized and it is possible that destruction of white and red blood cells in pleural effusion can cause an increase in the fluid cholesterol level. (B) Increased pleural permeability causes cholesterol concentrations to increase.

Measurement of pleural cholesterol >45 mg/dl has been used to improve the accuracy of differentiating transudative and exudative effusion [35].

Another study done in Catholic University hospital, Santiago, Chile [36] Marina Costa found sensitivity and specificity of following parameters for exudative pleural effusion as 98 and 82% (criteria by Light et al.), 90 and 100% (pCHOL >45 mg/dl) and 99 and 98% (by pCHOL+ pLDH >200 IU/l), respectively.

A study done by Hamm et al., mean cholesterol level in malignant effusions was 94 mg/dl, 76 mg/dl in inflammatory effusions and 30 mg/dl in the transudates. Using a dividing line of 60 mg/dl to separate the exudates from transudates, only 5% were incorrectly classified. Elevated cholesterol levels in exudates seem to be independent of serum levels [34].

Using pleural fluid, cholesterol levels at a cut-off point of greater than 60 mg/dl and/or total protein at a cut-off point of greater than 3 g/dl for distinguishing transudates and exudates, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), were 100% in a study done by Patel and Choudhury [37].

Brett reviewing Eid et al. CHEST 2002 Nov, most but not all, exudative effusions in CHF patients have causes other than heart failure. The authors believe that, in some cases with no apparent cause other than CHF, transudates might be 'converted' into exudates by traumatic taps (which lead to increased pleural fluid lactate dehydrogenase—itsself a criterion for an exudate) or by aggressive diuresis (which might transiently increase protein and LDL cholesterol concentrations in pleural fluid). In patients with previous bypass surgery, persistent impairment of lymphatic clearance might predispose to exudative effusions [38].

Pleural fluid cholesterol is better than Light's criteria for the differentiation of transudates and exudates and is less cumbersome as it does not require a simultaneous blood sampling. Cut-off value of pleural fluid cholesterol for differentiating transudates and exudates should be 45 mg/dl [39]. In this study, the sensitivity, specificity, positive predictive value and negative predictive value of the pleural fluid cholesterol (cut-off >45 mg/dl) were 97.06, 94.74, 97.06 and 94.74%, respectively, for identifying exudates.

NT-proBNP has been shown to correctly diagnose congestive heart failure as a cause of most effusions that have been misclassified as exudates by Light's criteria. Use of this test may therefore avoid repeated invasive investigations in patients where there is a strong clinical

suspicion of cardiac failure. The cut-off value however, varied widely from 600 to 4000 pg/ml (with 1500 pg/ml being most commonly used), and most studies excluded patients with more than one possible etiology for their effusion [40].

The findings in a study done by Mehdi Kashmiri showed taking a value of pleural cholesterol >55 mg/dl and pleural/serum cholesterol >0.3 to define exudative effusion resulted in less erroneous classification with a sensitivity of 93%, a specificity of 100%, a positive predictive value (PPV) of 100% and an accuracy of 95.2%. Using Light's criteria gave a sensitivity of 95%, a specificity of 95%, a PPV of 97.6% and an accuracy of 95.2%. Using cholesterol in differentiating exudate from transudate was especially useful in patients with congestive heart failure who received diuretics [41].

There are other biochemical parameters other than pleural fluid cholesterol to identify the exudative pleural effusions. The difficulties in classifying pleural fluid effusion are wiped away with few parameters other than cholesterol.

It has been observed that increase in uric acid level was present in pleural fluid of transudative pleural effusion than exudative pleural effusion. The optimum cut-off level for pleural fluid uric acid was 5.35 mg/dl with sensitivity of 89.32% and specificity of 92.60% [42]. Increase in uric acid in pleural fluid can be regarded to be a manifestation of tissue hypoxia [43]. Most of the patients with reasons to produce transudative effusion had oxidative stress or hypoxemia to explain the increased uric acid synthesis. The respiratory tract, indeed, remains a major target of oxidative damage caused by both endogenous and exogenous processes [44, 45]. The major causes of tissue damage associated with chronic inflammatory lung disease are the reactive species produced by phagocytes.

Metintas et al. [46] stated that the binding of uric acid is minimal to plasma protein and it is diffuse freely to different compartments. They suggested that the increase permeability, due to change in pleural-capillary pressure in formation of transudate, is the cause of the increase of uric acid levels in pleural fluid. So all these factors explains why uric acid level increases in transudative condition than exudative one.

In cases where no cause for an exudative effusion can be identified or CHF suspected, the sequential application of the fluid LDH, followed by the serum to pleural fluid protein (SF-P) and then the serum to pleural fluid albumin (SF-A) gradients, may assist in reclassifying pleural effusions as transudates [47].

Leers Mathie P.G. from Netherlands [48] found that combination of the parameters: pleural cholesterol and pleural LDH had accuracy of 98%, sensitivity of 98% and 95% specificity for diagnosing exudative pleural effusion compared that calculated by light's criteria being accuracy of 93%, sensitivity 100% and specificity 73%.

5. Conclusion

A pleural effusion (PE) is present when there is an excess fluid in the pleural space. It indicates an imbalance between pleural fluid formation and its removal. Pleural fluid is formed from the systemic vessels of the pleural membranes at an approximate rate of 0.6 ml/h and is

absorbed at a similar rate by the parietal pleural lymphatic system [6]. Pleural fluid accumulates due to local factors, systemic factors or translocation of fluid. At normal circumstances, pleural fluid entering the pleural space from the capillaries in the parietal pleura is removed by the lymphatics which can absorb 20 times more fluid than is formed.

Pleural fluid accumulates in settings of increased hydrostatic pressure, increased vascular permeability, decreased oncotic pressure, increased intrapleural negative pressure and decreased lymphatic drainage. On the basis of pathophysiology, pleural effusion can be transudates or exudates. It is important to classify the pleural fluid for diagnosis and appropriate management. Transudates occur when the mechanical factors influencing the formation or reabsorption of pleural fluid are altered, like a decrease in plasma or elevated systemic or pulmonary hydrostatic pressure. Exudates results from inflammation or irritation or other disease processes involving pleura resulting in increased permeability.

Light et al. found criteria to have sensitivity and specificity of 99 and 98%, respectively, for differentiating transudative and exudative PEs (ratio of protein in pleural fluid and serum >0.5 ; ratio of LDH in pleural fluid and serum >0.6 and pleural fluid LDH $>2/3$ rd of upper limit of serum LDH) [20]. It is found that 25% of patients with transudates pleural effusion are mistakenly identified as having exudative effusion by Light's criteria. In cases of heart failure on diuretic therapy, the transudative pleural effusions have high protein. Pleural cholesterol is thought to be derived from degenerating cells and vascular leakage from increased permeability. The cause of the increased cholesterol concentration is unknown, but two hypotheses are available: one states that cholesterol production by different cells has been recognized and it is possible that destruction of white and red blood cells in pleural effusion can cause an increase in the fluid cholesterol level and second relates with increased pleural permeability that causes cholesterol concentrations to increase.

Pleural fluid cholesterol as proposed by Heffner's meta-analysis can diagnose exudative pleural effusion without need of serum values. This can avoid the financial burden and double pricks (serum and pleural fluid) in anxious patients to go through the series of tests to confirm the exudative pleural effusion. With a classifying threshold of 1.16 mmol/l, pCHOL has a sensitivity of 97.7% and specificity of 100% for diagnosis of exudates with accuracy of 98.3% compared to Light's criteria (98% sensitivity and 82% specificity). pCHOL is highly correlated than protein ratio with clinical diagnosis for exudates [29]. Moreover in pleural effusion with etiologies as transudates, parapneumonic, tubercular and neoplastic pleural effusion, pCHOL levels were 0.53 ± 0.28 , 1.81 ± 0.59 , 2.08 ± 0.58 and 1.58 ± 0.65 mmol/L, respectively.

Study done by Leers Mathie PG, it was found that pleural cholesterol and pleural LDH had accuracy of 98%, sensitivity of 98% and 95% specificity for diagnosing exudative pleural effusion compared that calculated by light's criteria being accuracy of 93%, sensitivity 100% and specificity 73% [47].

It is concluded that pCHOL has a better sensitivity, specificity and accuracy in differentiating transudates and exudates than the parameters of Light's criteria. This also avoids the plasma protein and gradients, sLDH, pleural fluid protein and LDH. Therefore it is more efficient, easier and more cost effective method to differentiate exudates from transudates. This study also suggests that determination of pCHOL should be in routine practice in cases of pleural effusion.

Conflict of interest

There is no conflict of interest in this chapter.

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