Pleural Fluid, Transudate and Exudate

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Abstract

Pleural effusion is a common clinical problem. In the normal state, the pleural cavity is bathed in a small volume of physiologic pleural fluid containing mainly macrophages and lymphocytes. The volume of the pleural fluid can increase dramatically with most pathologic conditions affecting the pleura. The pleural effusion will alter the respiratory mechanics, commonly resulting in dyspnea. It is useful to differentiate the pleural effusion into transudates and exudates. Traditionally, such differentiation is made using Light’s criteria, based on the protein and lactate dehydrogenase levels in pleural fluid and serum. Transudates occur as a result of altered hydrostatic and/or oncotic pressures and are usually secondary to congestive cardiac failure or hepatic cirrhosis. Exudates develop as a result of plasma extravasation, which is at least in part due to pleural or pulmonary inflammation. Evidence suggests that cytokines, such as vascular endothelial growth factor, play a role in exudative effusion formation. Parapneumonic effusion, malignant effusion, and tuberculous pleuritis are the most common causes of exudative effusions worldwide.

Pleural Fluid Formation in the Normal State

In the healthy state, the pleural cavity – which is extremely thin (10 μm) but has a large surface area (1–2 m²) – contains a small amount of fluid that serves as a lubricant to facilitate the gliding of the visceral pleura over the parietal pleural membrane. This fluid is a transudate and contains mainly macrophages.

Most of the knowledge on the volume, composition, and dynamics of normal pleural fluid has been obtained in animal studies, and very few human studies are available. Pleural fluid volume assessment in normal circumstances can be performed using direct measurements (e.g., gentle aspiration after pleural puncture, pleural catheterization, or even thoracotomy) or using indirect techniques (e.g., pleural lavage).

The normal physiologic pleural fluid is formed by filtration from systemic vessels and occurs predominantly at the less dependent region of the pleural cavity, where the blood vessels are closest to the mesothelial surface. The systemic blood supply from the intercostal arterial circulation of parietal pleura is believed to be the principal source of this fluid. In humans, the bronchial circulation of the visceral pleura is not likely to contribute significantly because the human visceral pleura is thick and the microvascular pressure for fluid filtration in the bronchial circulation is low (relative to that of the parietal intercostal circulation). Water filters into the pleural space according to the net hydrostatic–oncotic pressure gradient. Water and small molecules (<4 nm) pass freely between the mesothelial cells. Larger molecules can be actively transported through the mesothelial cells via a transcytoplasmatic pinocytic mechanism. This mechanism probably also contributes to liquid and protein exchange in the pleural space, although its overall contribution is unclear.

Direct measurements of normal pleural fluid volume in various animal models (e.g., rabbits, dogs, and sheep) consistently show volumes between 0.04 and 0.12 ml kg⁻¹ per pleural space. Differences in measurement results are caused by the various methodologies used and by the fact that the fluid volume adherent to the lung surface has not always been included. In humans, one direct measurement study by Yamada (puncture of the pleural space in the 9th or 10th intercostal space at the posterior axillary line) yielded some fluid in one-third of normal individuals. Interestingly, after exercise, up to two-thirds of individuals had detectable pleural fluid. Most often, only some foam was retrieved, but in some individuals up to 20 ml of fluid was collected. In another study, a pleural lavage procedure was performed in normal subjects undergoing thoracoscopy for treatment of sympatetic disorders. Estimation of the volume of the original pleural fluid present was performed using the urea dilution method, based on the principles of dilution and mass conservation. The volume of the original fluid present in each hemithorax was 0.13 ± 0.06 ml kg⁻¹ body mass.

The biochemical composition of normal pleural fluid resembles that of other interstitial fluids. The
concentration of small molecules (e.g., glucose and urea) is similar to that of serum, whereas the concentration of macromolecules such as protein or lactate dehydrogenase is less than half of that found in serum (transudate by Light's criteria).

In normal pleura, the production of physiologic pleural fluid is estimated to be approximately 0.01 ml kg\(^{-1}\) h\(^{-1}\) in sheep and 0.02 ml kg\(^{-1}\) h\(^{-1}\) in rabbits, which extrapolates to 17 ml day\(^{-1}\) in a 70-kg man. The half-life of fluid turnover in sheep and rabbits is 6–8 h.

Fluid exits the pleural cavity via the stomata (diameter, 2.5–10 \(\mu\)m) on the parietal pleura, which empty into lymphatic channels by bulk flow such that liquid and protein are evacuated at the same rate. Hence, the protein concentrations of the residual pleural fluid remain constant. The drainage capacity in normal pleura is large (approximately 0.2–0.3 ml kg\(^{-1}\) h\(^{-1}\)) and can increase up to 30-fold over the normal rate of drainage after a pleural fluid load.

The cellular composition of normal pleural fluid has mainly been studied in animal models. Total white blood cell counts varied between 1216±800 and 2442±595 cells \(\mu\)l\(^{-1}\), mostly consisting of macrophages/monocytes. Other free cell populations included mesothelial cells and lymphocytes. Using the direct measurement method, Yamada and colleagues found that in physiologic human pleural fluid, the total white blood cell count was 4500 cells \(\mu\)l\(^{-1}\), with a differential cell count of 53.7% monocytes/macrophages, 10.2% lymphocytes, 3.6% granulocytes, and 3% mesothelial cells (and 29.5% deteriorated cells of unclear classification). In a human pleural lavage study, the concentration of white blood cells in the physiologic pleural fluid was 1716 cells \(\mu\)l\(^{-1}\). In nonsmoking subjects, the leukocytes consisted of 75% macrophages (median, interquartile range (IR), 64–80%), 23% lymphocytes (IR, 18–36%) with a CD4:CD8 ratio of 0.75 (IR, 0.6–1%), and 1% free mesothelial cells (IR, 0–2%). Neutrophils and eosinophils were only sporadically seen. Interestingly, there was a small but significant increase in neutrophils in smokers. Mesothelial cells, macrophages, lymphocytes, eosinophils, and neutrophils are thought to play a role in the defense of the pleural space and may be involved in the generation of a variety of inflammatory responses. Pleural cells are essential participants in the development of pleural pathologies, including inflammatory and metastatic diseases.

### Pleural Fluid Formation in Pathologic States

A pleural effusion usually refers to an abnormal accumulation of pleural fluid. The pleural space is under subatmospheric pressure and can accommodate a large volume of fluid, partly through alteration of the chest wall and diaphragm mechanics and through compression of the underlying lung.

Pleural fluid accumulates when the rate of pleural fluid formation exceeds the rate of pleural fluid removal (Table 1). Most effusions develop from both increases in pleural fluid entry and decreases in fluid exit rates. In the presence of the normal fluid absorption capacity, fluid formation has to increase by more than 30-fold, and remain at that rate, to create an effusion. On the other hand, decreased removal of the fluid alone is unlikely to result in significant accumulation of pleural fluid, given that the normal rate of pleural fluid formation is only approximately 17 ml day\(^{-1}\). Hence, often abnormalities in production as well as absorption mechanisms are present in patients with pleural effusions.

The most common cause of increased pleural fluid formation is increased interstitial fluid in the lung, which can result either from changes in the pressure gradients producing a transudate with a low protein concentration or from changes in vascular permeability producing an exudate with a high protein level. Twenty percent of interstitial fluid leaves the lung via the pleural space. Starling’s equation dictates the movement of fluid across the pleural capillaries, and therefore increased intravascular pressures, increased pleural fluid protein levels, and decreased intrapleural pressures can all contribute to pleural fluid formation.

Increased pleural fluid formation also results from pleural inflammation. Exudates form from a vascular bed with a high leakiness to protein. Inflammation or

<table>
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<th>General causes of pleural effusions</th>
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<td>Increased pleural fluid formation</td>
<td>Increased interstitial fluid in the lung</td>
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<td>Increased permeability of the capillaries in the pleura</td>
<td>Right or left ventricular failure, pneumonia, and pulmonary embolus</td>
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<td>Increased levels of VEGF</td>
<td>Increased intravascular pressure in pleura</td>
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<tr>
<td>Increased pleural fluid protein level</td>
<td>Increased permeability of the capillaries in the pleura</td>
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<td>Decreased pleural pressure</td>
<td>Pleural inflammation</td>
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<td>Lung atelectasis or increased elastic recoil of the lung</td>
<td>Increased levels of VEGF</td>
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<td>Increased fluid in peritoneal cavity (if diaphragm communications exist)</td>
<td>Peritoneal dialysis</td>
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<td>Ascites or peritoneal dialysis</td>
<td>Disruption of the thoracic duct (chylothorax)</td>
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<tr>
<td>Disruption of blood vessels in the thorax (hemothorax)</td>
<td>Disruption of the thoracic duct (chylothorax)</td>
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<td>Decreased pleural fluid absorption</td>
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injury to the vascular bed enhances the vascular permeability, resulting in the accumulation of fluids of high protein concentrations (exudates). Pleural effusion can also occur from transdiaphragmatic migration of ascites, from disruption of the thoracic duct (chylothorax) or an intrathoracic blood vessel (hemothorax), or from a fistula draining other body fluids from extrapleural organs (e.g., urinothorax from a renal fistula).

The most common cause of decreased pleural fluid absorption is obstruction of the lymphatics draining the parietal pleura. This can occur in the parietal pleura if the pleura is inflamed, such as with tuberculous pleuritis or parapneumonic effusion, or in the lymph nodes, such as with malignant effusions when the nodes are involved with tumor.

**Transudate and Exudate**

When faced with a patient with abnormal pleural fluid accumulation, a useful first step is to determine if the effusion is a transudate or exudate. This helps to provide insight into the etiology (and differential diagnosis) of the pleural effusion.

Transudative effusions, most commonly due to cardiac failure or hepatic cirrhosis, accumulate from imbalances in hydrostatic and oncotnic pressures, such that excessive pleural fluid formation saturates the drainage capacity of the pleural cavity. Exudates accumulate due to increased vascular permeability, often (but not necessarily) with a concomitant reduction in fluid reabsorption. Parapneumonic pleural effusions, tuberculous pleuritis, and malignant pleural effusions account for most of the exudative effusions.

Most commonly, differentiation between transudative and exudative effusions is made using Light’s criteria. A pleural effusion is an exudate if it satisfies any of the following criteria. Conversely, a transudate is one that meets none of the criteria:

- pleural fluid:serum protein ratio > 0.5;
- pleural fluid LDH more than two-thirds of the upper limit of normal serum LDH; and
- pleural fluid:LDH ratio > 0.6.

Light’s criteria have a high sensitivity for the diagnosis of exudates. False positives are known to occur. In particular, patients with transudative effusions who are on diuretics may have a pleural:serum protein ratio > 0.5. In such a situation, the protein gradient (serum–pleural fluid protein) > 3.1 g.dl$^{-1}$ would define a true transudate. The diagnosis of pleural effusions and their clinical presentation and management are discussed elsewhere in this book.

**Immunologic Basis of Pleural Effusion Formation**

Increased fluid formation is the principal underlying abnormality in the genesis of most exudative effusions. None of the available strategies for managing recurrent effusions, such as pleurodesis or pleurectomy, targets directly against pleural fluid formation. Various molecules have been proposed as having a pathogenic role in pleural effusion formation, of which vascular endothelial growth factor (VEGF) has attracted the most attention. There is compelling evidence that VEGF promotes angiogenesis and tumor growth, and various anti-VEGF strategies are in clinical trials.

VEGF is present in significant quantities in pleural and peritoneal effusions of varying etiologies, especially in malignant effusions, empyemas, ovarian hyperstimulation syndrome, and Meigs’ syndrome. Local pleural or peritoneal production of VEGF from residual mesothelial cells and infiltrating cells, such as inflammatory cells and malignant cells, is believed to be the main source of VEGF in exudative effusions.

VEGF production can be stimulated by various cytokines, among which transforming growth factor-$\beta$ appears to be the most potent and consistent, both in vitro and in vivo. *Staphylococcus aureus*, as well as the resultant hypoglycemia and acidosis, can stimulate mesothelial release of VEGF and may explain why VEGF levels are high in empyema.

Animal experiments have confirmed the essential role of VEGF in malignant pleural effusion and in ascites accumulation. Promising results are accumulating on the use of VEGF inhibition (e.g., neutralizing anti-VEGF antibodies, VEGF receptor phosphorylation blockade, and antibodies against KDR/Flik-1 receptors) in reducing vascular permeability and malignant effusion formation in animal studies. If these results can be reproduced in clinical settings, anti-VEGF therapy would represent a novel management strategy for recurrent pleural effusions.

**Animal Models for Pleural Effusion Studies**

Many animal models have been employed to study the mechanisms of pleural fluid formation and
absorption and the associated physiologic changes in the pleural cavity. Transudate formation from heart failure has been studied by creating volume overload in anesthetized ventilated sheep. Fluid transferred from lung parenchyma into the pleural space was collected by wrapping a bag around the exposed lung. Such experiments confirmed that the pleural space provided an important route of clearance of pulmonary edema. A murine model of renal failure and fluid overload has been described by ligating the renal vessels followed by intraperitoneal instillation of isomolar saline. A measurable amount of pleural fluid can be collected after 3 h. This model has been used to study the role of aquaporin water channels in pleural fluid transport, but it can easily be extended to study other aspects of pleural effusion secondary to renal failure.

Removal of pleural fluid and particulates from the pleural space has been studied in sheep, rabbits, and, occasionally, dogs using radioactive- or fluorescent isothiocyanate-labeled tracers to follow the protein efflux and reabsorption. Potential drawbacks of these animal studies include the variations in the anatomy and probable differences in the pleural fluid exchange mechanisms between humans and animals.

In humans, effusions usually accumulate secondary to various pleural pathologies. Specific animal models have been used to simulate human pleural diseases, including models for malignant effusions (commonly by intrapleural implantation of cancer cells in athymic nude mice) and bacterial empyema (usually in rabbits using Pasteurella multocida). Direct injection of carrageenan into the pleural cavity of animals (e.g., mouse, rat, or rabbit) has often been employed to generate pleural inflammation and exudative pleural effusions for investigations. Although less commonly used, animal models have also been designed for tuberculous pleuritis, rheumatoid pleuritis, effusions from esophageal rupture, etc.

**Physiologic Sequelae of Pleural Fluid**

When pleural fluid is present, its volume must be compensated for by an increase in the size of the thoracic cavity, a decrease in the size of the lung or heart, or a combination of these. The presence of pleural fluid usually leads to an increase in pleural pressure. As a result of this increase, the distending pressures of the lung and heart are decreased while the distending pressure of the thoracic cavity is increased.

**Effects on Pulmonary Function**

When a thoracentesis is performed on a patient with a pleural effusion, the forced vital capacity and the forced expiratory volume in 1 s (FEV₁) will each increase, on average, approximately 200 ml for every liter of pleural fluid removed. The increase in the total lung capacity is almost twice the increase in FEV₁.

The explanation for this relatively low increase in the pulmonary function test results is that in addition to the lung increasing in size, the thorax decreases in size and the diaphragm moves up after fluid evacuation. However, there is much interindividual variation. The increase in pulmonary function is greater in patients with higher initial pleural pressure and in patients with smaller changes in the pleural pressure as fluid is removed.

**Effects on Blood Gases**

Most patients with more than minimal pleural effusions have abnormal arterial blood gases, primarily a low PaO₂. However, the arterial blood gas results do not improve much and may even deteriorate when a thoracentesis is performed. The main mechanism underlying the arterial hypoxemia is an intrapulmonary shunt, which does not change significantly after thoracentesis.

**Effects on the Diaphragm**

The presence of pleural fluid profoundly affects the diaphragm because of the weight of the fluid on the diaphragm. The degree of dyspnea with a pleural effusion is related to its effect on the diaphragm. The patient usually is not dyspneic if the diaphragm is domed and is functioning normally, the patient usually has some dyspnea if the diaphragm is flattened and does not move with respiration, and the patient usually has severe dyspnea if the diaphragm is inverted.

**Effects on the Heart**

In spontaneously breathing dogs, right ventricular diastolic collapse begins when the mean pleural pressure is increased by 5 mmHg. If the mean pleural pressure is increased by 15 mmHg, the stroke volume decreases by approximately 50%, and the cardiac output decreases by 33%. Although there have been few studies on the effects of pleural fluid on the heart in humans, there have been several case reports in which the presence of a pleural effusion has compromised cardiac output.

**Summary**

The abnormal accumulation of pleural fluid is a common clinical presentation and can occur in association with a wide range of pulmonary and extrapulmonary diseases. In health, the pleural cavity
contains a small amount of fluid for lubrication. The volume of the pleural fluid can increase dramatically with various pleural diseases. The respiratory mechanics are altered to accommodate the extra volume of fluid, resulting in dyspnea. Categorizing the effusion into transudates and exudates using Light’s criteria may provide insight on the etiology and pathogenesis of the effusion. Congestive cardiac failure, hepatic cirrhosis, and renal failure are the most common causes of transudative effusions, whereas infective (including tuberculosis) and malignant pleural diseases account for a majority of exudative pleural effusions. Research on the immunologic basis of pleural vascular hyperpermeability may provide novel strategies for future management of recurrent exudative effusions.

See also: Mesothelial Cells. Pleural Effusions: Overview; Pleural Fluid Analysis, Thoracentesis, Biopsy, and Chest Tube; Parapneumonic Effusion and Empyema; Malignant Pleural Effusions; Pleural Fibrosis; Chylothorax, Psuedochylothorax, LAM, and Yellow Nail Syndrome; Hemothorax. Pleural Space. Signs of Respiratory Disease: Lung Sounds. Vascular Endothelial Growth Factor.

Further Reading


