Clinical overview of the physiology and pathophysiology of pleural fluid movement: a narrative review

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Applying the basics of the pathophysiology of pleural fluid movement to clinical practice, with the information provided by a pleural fluid and pleural tissue analysis, can help understand the heterogeneity of the pleural response and the aetiology of PE https://bit.ly/3xWl9F9

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Abstract

In physiological conditions, the pleural space couples the lung with the chest wall and contains a small amount of fluid in continuous turnover. The volume of pleural fluid is the result from the balance between the entry of fluid through the pleural capillaries and drainage by the lymphatics in the most dependent areas of the parietal pleura. Fluid filtration is governed by Starling forces, determined by the hydrostatic and oncotic pressures of the capillaries and the pleural space. The reabsorption rate is 28 times greater than the rate of pleural fluid production. The mesothelial layer of the inner lining of the pleural space is metabolically active and also plays a role in the production and reabsorption of pleural fluid.

Pleural effusion occurs when the balance between the amount of fluid that enters the pleural space and the amount that is reabsorbed is disrupted. Alterations in hydrostatic or oncotic pressure produce a transudate, but they do not cause any structural damage to the pleura. In contrast, disturbances in fluid flow (increased filtration or decreased reabsorption) produce an exudate *via* several mechanisms that cause damage to pleural layers. Thus, cellular processes and the inflammatory and immune reactions they induce determine the composition of pleural fluid. Understanding the underlying pathophysiological processes of pleural effusion, especially cellular processes, can be useful in establishing its aetiology.

Introduction

Pleural effusion (PE) is a common clinical problem with >60 recognised causes, including local pleural processes, underlying lung, systemic and multi-organ dysfunction, and drug-induced disease [1]. Its prevalence is around 400 cases/100 000 inhabitants [2]. It is estimated that 1.5 million PEs are diagnosed annually in the United States [3]. This means that most clinicians will have to manage cases of PE in the course of their careers. Without a deep understanding of the pathophysiology of PE, establishing an accurate diagnosis that ensures optimal management can be challenging. In the light of these difficulties, sophisticated diagnostic procedures that require extensive skills and training have been developed for PE [4]. As a result, some centres have created dedicated pleural disease units [5].

This challenging situation, added to the increasing clinical and economic burden of pleural diseases [6], makes it necessary that clinicians thoroughly understand the physiology and pathophysiology of pleural fluid (PF) movements and their clinical applications. In clinical practice, when analysing a PF of unknown origin, the first step is to be aware of these mechanisms, followed by being able to produce a thorough clinical record and perform a careful physical examination. Subsequently, the data obtained will help the clinician determine whether it is necessary or not to perform specific laboratory tests or pleural procedures for a final diagnosis.

Physiology of PF movement

The pleural space is the system that couple the lung to the rib cage. Pressure in the pleural space (pleural surface pressure) plays an important role in cardiopulmonary physiology. Pleural surface pressure results from the opposing pressure of the outer surfaces of the lungs and heart and the pressure of the inner surface of the thoracic cavity. These structures are distensible; their volume depends on the pressure gradient between their inner and outer structures, as well as on their compliance. Hence, pleural surface pressure is useful for determining the volume of these organs.

Under normal conditions, the pleural space contains a small amount of fluid, with a low protein content [7]. This fluid originates from the pleural capillaries and reaches the pleural space *via* microvascular filtration [8]. To reach the pleural space, PF and the proteins it contains cross two barriers: the capillary endothelium (the main resistance to fluid and protein movement) and the pleural interstitium (or membrane). The filtration of PF and solutes from the circulation into the pleural space is governed by two equations. The first is Starling's equation, which considers the difference in hydrostatic and oncotic pressures between the pleural capillaries and the pleural space [9]. The second is the solute flux equation, based on the capacity of diffusion of each solute, which depends on the filtration coefficient, surface area ($\sim$4000 cm^2 in a 70 kg man) and thickness of the membrane. The drag reflection coefficient of each solute is also considered in the solute flux equation [10]. In parallel to electrolyte absorption, there is also a small active transport by which the two mesothelial layers absorb fluid [11].

$$\text{Starling equation: } PFM = K[(CAPhp - PLEhp) - (CAPop - PLEop)].$$

where PFM, represents pleural fluid motion; K, pleural filtration coefficient; CapHP, capillary hydrostatic pressure; PLEhp, pleural hydrostatic pressure; CAPop, capillary oncotic pressure; and PLEop, pleural oncotic pressure.

Experimentally it has been observed that the physiological PF pressure is lower (more negative) than the pleural surface pressure. At the bottom of the thoracic cavity, PF pressure is only slightly lower than the surface pressure. This difference increases progressively as we ascend in the thoracic cavity. If PF behaved as a continuous system with homogeneous thickness and remained in static equilibrium, for a column of liquid with a gravimetric density of 1 $g \cdot mL^{-1}$, the vertical difference in hydrostatic pressure should be 1 $cmH_2O \cdot cm^{-1}$ height. However, the fluid pressure gradient has been found to range from 0.14 to 0.80 $cmH_2O \cdot cm^{-1}$ height [12]. In contrast, the surface pressure gradient is -0.2 $cmH_2O \cdot cm^{-1}$ height [13]. Hence, pleural surface pressure would vary with height in the pleural space according to PF pressure, regional deformation of pleural surface (at the contact points between the two pleural sheets) and weight of the lung, which is higher in the dependent regions of the lung [14]. Therefore, there must be a gravitational flow of fluid in the pleural cavity from the apex to the base of the lung. As a result, differences between PF and surface pressures will be greater at high lung volumes [15]. One theory to explain the difference between the surface pressure and the pressure of the PF would be that, at functional residual capacity, the thickness of the PF ranges between 6 and 15 µm and there are cells with a similar diameter in it. Therefore, at this lung volume, these cells will be trapped between both pleural surfaces and will produce local deforming forces in the pleura. If lung volume increases, the thickness of the PF will decrease, more cells will be trapped and more deforming forces will be created. Furthermore, it must be taken into account that the mesothelial cells on both pleural surfaces have abundant microvilli about 3 µm in length. When the thickness of the PF is less than this length, the microvilli will impact the opposite pleural leaf, creating more deforming forces and further reducing the pressure of the PF.

Under normal conditions, the volume of PF in the pleural space is the result of a dynamic equilibrium between fluid inflow and outflow. This equilibrium is maintained by the equations mentioned above and by lymphatic drainage. Drainage takes place through stomas (or openings) in the parietal pleura, which form lymphatic lacunae immediately beneath the mesothelial layer. The lacunae merge into collecting lymphatic vessels, which join the vessels of the intercostal trunk and direct the flow mainly to the mediastinal lymph nodes [11, 16]. The pleura is a thin membrane consisting of five layers, including an outer fibroelastic layer; a highly vascularised layer of loose subpleural connective tissue; an inner layer of elastic tissue; a submesothelial layer of loose connective tissue; and a mesothelial cell layer [17]. The structure of these cells is similar to that found in the serous membranes of a wide variety of animals [17]. In addition to providing a passive lining to serous cavities, the mesothelium of the inner lining of the pleural space, which is metabolically active, is involved in cellular and humoral immunity and plays an active role in the production and reabsorption of PF [18, 19].

The fluid in the pleural space is continuously exchanged and forms a small film about 10 µm thick between the parietal and the visceral pleura [17] that allows one membrane to slide over the other. This lubrication is provided by hyaluronic acid-rich glycoproteins trapped in the microvilli of the mesothelium and provides a low coefficient of friction [20]. Under physiological conditions, $1–2\times10^3$ cells·mL^{-1}, usually macrophages, are found in this fluid. The PF filtered through the parietal pleura generates a higher pressure gradient than that coming from the visceral pleura. The reason for this difference is that the capillaries of the parietal pleura receive blood from the systemic circulation, whereas those of the visceral pleura receive it from the pulmonary circulation [21]. In other words, in a normal situation, the parietal pleura plays a more relevant role in the filtration of fluid into the pleural space than the visceral pleura [22].

The characteristics and volume of PF are subject to a number of dynamic phenomena that influence systemic and pulmonary circulation, lymphatic drainage, and rib cage and heart movements [23]. Studies in animal models have revealed that, under normal conditions, the net rate of PF formation is ≈0.01 mL·kg^{-1}·h^{-1}, hence, in a 60-kg person, about 15 mL·day^{-1} would enter. In contrast, its reabsorption is ≈0.28 mL·kg^{-1}·h^{-1} [24, 25]. In the healthy subject, as a result of the balance between hydrostatic and oncotic pressures between the pleural space and the visceral pleura, the net fluid flow through this membrane is virtually zero. It must be taken into account that the physiological PF in the pleural space also has oncotic and hydrostatic pressure. This hydrostatic pressure is negative at functional residual capacity due to balance between the elastic lung recoil force, which tends to retract the lung, and the rib cage, which tends to expand it (figure 1a). Therefore, fluid primarily filtrates through the parietal pleura, since, as described above, hydrostatic pressure is higher in the pleural capillaries than in the visceral pleura. Once in the pleural space, PF flows towards the lower parts for the aforementioned reasons and is reabsorbed by the lymphatics of the parietal pleura; lymphatics are located in the most dependent regions on this membrane, mainly in the diaphragmatic and mediastinal regions [10]. The lymphatics of the visceral pleura join the mediastinal lymphatics and only drain lymph from the lungs, as they have no contact or communication with the pleural space [26].

Pathophysiology of PF movement

For a PE to develop, one of the following situations must occur: the amount of fluid passing into the pleural space must be 30 times greater than normal to exceed the rate of lymphatic reabsorption; or lymphatic reabsorption is significantly decreased. Patients with heart failure are a typical case where the two situations occur simultaneously [27]. There are several mechanisms by which one of these situations may occur (table 1).

Increased hydrostatic pressure in the capillaries of the visceral pleura

Patients with heart failure are a typical case in which increases in systolic and diastolic pressures of the left ventricle result in increased wedge pressures of the pulmonary capillaries and therefore an increase in hydrostatic pressures within the capillaries of the visceral pleura that causes fluid to move into the pleural space [28] (figure 1b). Determination of natriuretic peptides secreted by the cardiac ventricles in response to their acute distension may be useful in the diagnosis of these effusions [29].

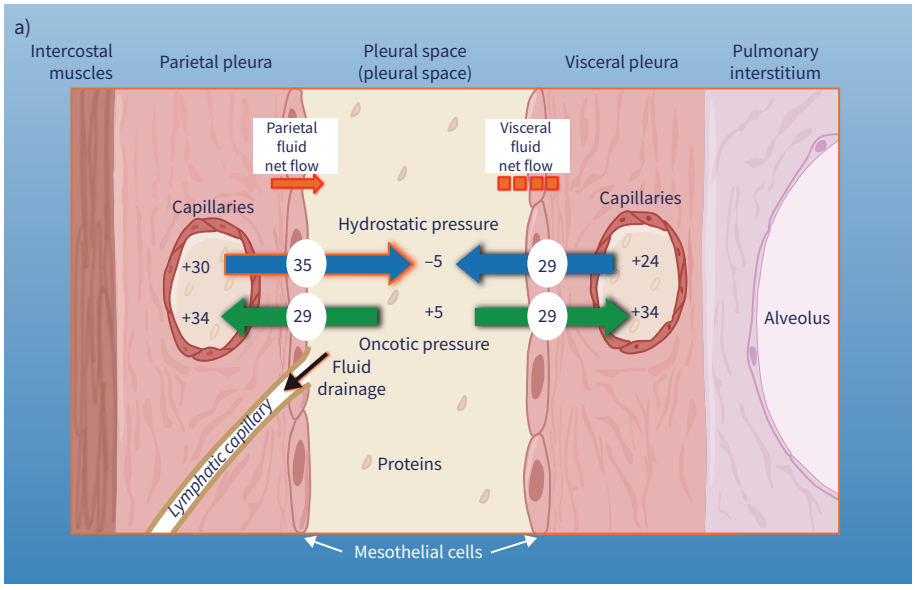
Decrease in oncotic pressure in pleural capillaries

This phenomenon occurs in patients with hypoalbuminaemia, or with excessive protein loss from the renal glomerulus (in nephrotic syndrome, for example) [30, 31]. In these cases, the small amount of solutes in the pleural capillaries causes a decrease in oncotic pressure, which reduces the attraction of fluids into the capillaries. As a result, fluid accumulates in the pleural space. This fluid mainly comes from the parietal pleura, although the visceral pleura may also contribute. Clinically, this mechanism is a rare cause of large PE, probably due to residual lymphatic reabsorption.

Decrease in hydrostatic pressure in the pleural space

This type of PE occurs in the trapped lung. The hydrostatic gradient between the pleural space and the parietal pleura rises due to the increased negative pressure in the pleural space; as a result, the net flow of fluid into the pleural space increases to reduce the hydrostatic gradient (figure 1c). In this type of PE, as fluid is removed by thoracentesis, intrapleural hydrostatic pressure becomes even more negative and fluid builds up again in the pleural space [32]. In this situation, pleural elastance (change in PF pressure in cmH_2O/litre of fluid removed) increases (figure 2) [4, 33, 34].

These three mechanisms involve a change in pressure (hydrostatic or oncotic), which causes an amount of fluid to pass into the pleural cavity, thereby exceeding the reabsorption capacity of the lymphatics. This type of effusion is called transudate, and pleural membranes remain intact.


a)
Intercostal muscles
Parietal pleura
Pleural space (pleural space)
Visceral pleura
Pulmonary interstitium
Parietal fluid net flow
Visceral fluid net flow
Capillaries
Capillaries
Hydrostatic pressure
+30
35
−5
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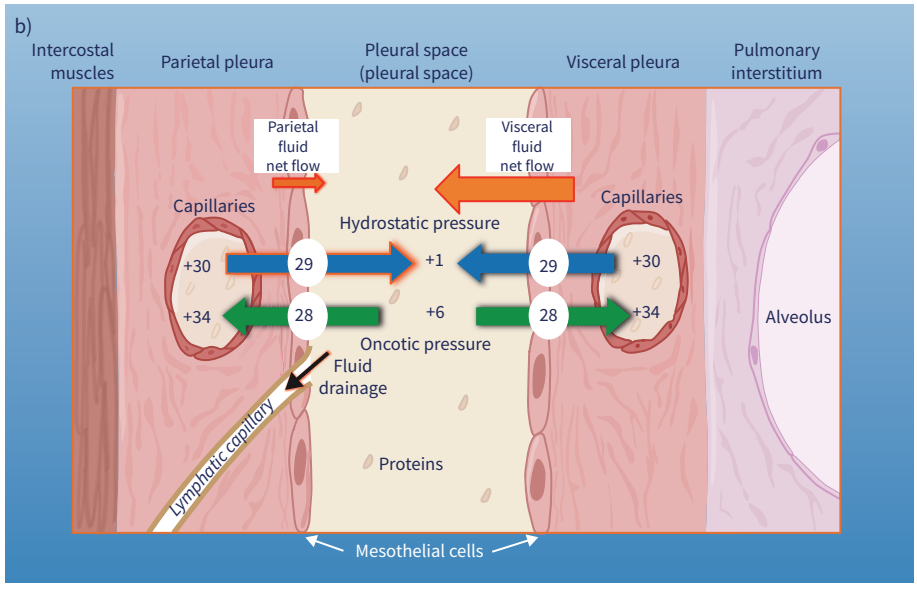
Alveolus
Oncotic pressure
Fluid drainage
Lymphatic capillary
Proteins
Mesothelial cells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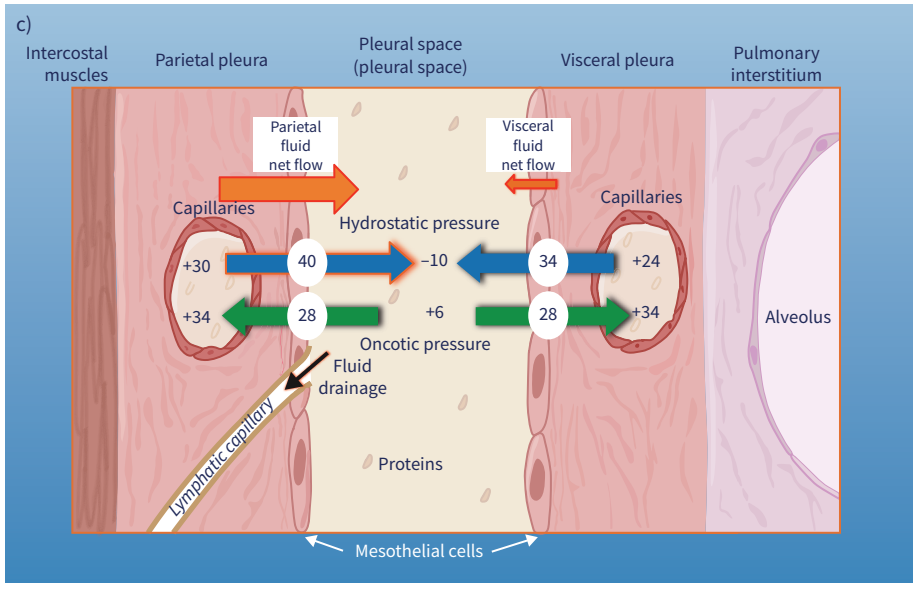
c)
Intercostal muscles
Parietal pleura
Pleural space (pleural space)
Visceral pleura
Pulmonary interstitium
Parietal fluid net flow
Visceral fluid net flow
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Alveolus
Oncotic pressure
Fluid drainage
Lymphatic capillary
Proteins
Mesothelial cells

FIGURE 1 Movement of fluid in the pleural space. Reproduced from [4] with permission of the Spanish Society of Pulmonology and Thoracic Surgery. a) Normal lung and pleura. The balance of the hydrostatic and oncotic pressure gradients of the pleural capillaries and pleural space favours the formation of pleural fluid, with a net flow of fluid from the parietal pleura and a balance in the visceral pleura (pressures in centimetres of H_2O). b) Heart failure. The pulmonary oedema that occurs in these cases increases the hydrostatic pressure in the capillaries of the visceral pleura and the fluid passes into the pleural space. c) Trapped lung. The visceral pleura is thick and fibrous due to a previous inflammatory process, which prevents expansion into the lung and leads to negative hydrostatic pleural pressure. This alteration of Starling forces leads to the formation of a transudative pleural fluid.

Increased permeability of pleural capillaries

This type of PE is called exudate because the pleura is diseased, resulting in an increased permeability of the pleural capillaries. This enables a greater amount of fluid and solutes to enter the pleural space. In exudates, it is the inflow and outflow that are altered, not pressures. Microvascular permeability may increase by the action of two mechanisms: the opening of new spaces between cells (where permeability to water and small solutes increases, but macromolecule filtration is still restricted) or the opening of transcellular pathways (in this case, permeability to macromolecules also increases). A variety of stimuli and mediators can cause these effects on the endothelium [35]. Pleural exudates contain some of the mediators involved in the increase of microvascular permeability, since activated mesothelial cells release a variety of chemokines, cytokines and growth factors [19, 36]. Increased permeability favours the entry of a variety of inflammatory cells into the pleural space, which also contributes to an increased production of mediators of mesothelial barrier dysfunction. The cellular mechanisms involved will differ depending on the disease causing the exudate, be it lung infection [37, 38], tuberculosis [39, 40] or neoplasia [19].

Impaired lymphatic drainage of the pleural space

It is caused by an obstruction somewhere in the lymphatic system, including the stomas and mediastinal lymph nodes, caused by fibrosis, a tumour (usually lymphoma or a mediastinal mass) or lymphatic dysfunction, as in yellow nail syndrome [31, 41] or lymphangioleiomyomatosis [42]. Both situations will cause a retrograde accumulation of fluid into the pleural space. Effusion is typically a serous exudate, although chronic obstruction of the lymphatic system may cause lymph to accumulate (chylothorax). In the absence of a trauma history, the most frequent causes of chylothorax include a malignant neoplasm and a variety of systemic diseases that occlude the thoracic duct and cause lymph to leak into the pleural space [43]. Most patients with chylothorax will have a unilateral PE, and the laterality will depend on the anatomical site of the chyle leak [44]. Occasionally, chylothorax is not due to lymphatic obstruction, but to portal hypertension and chylous ascites reaching the pleural space through diaphragmatic defects. In this case, the PF may be a transudate. Chylothorax has a typical milky appearance, although it may be absent, and has specific biochemical features that make it easily diagnosable [45].

Movement of fluid from the peritoneal space

Any disease involving the presence of fluid in the abdominal cavity can cause PE. Fluid may accumulate in the pleural space due to the pressure gradient between the peritoneal and pleural spaces (greater in the former as the latter has a negative pressure). This facilitates the unidirectional passage of fluid into the thoracic cavity and not the other way round. Fluid also filtrates through diaphragmatic defects, generally smaller than 1 cm, usually found in the tendinous part of the right diaphragm. In this case, the type of effusion (transudate or exudate) will depend on the disease that caused the accumulation of free fluid in the

TABLE 1 Mechanisms of production of a pleural effusion

Mechanism	Type of pleural effusion
Increased hydrostatic pressure in the capillaries of the visceral pleura	Transudate
Decrease in oncotic pressure in pleural capillaries	Transudate
Decrease in hydrostatic pressure in the pleural space	Transudate
Increased permeability of pleural capillaries	Exudate
Impaired lymphatic drainage of the pleural space	Exudate
Movement of fluid from the peritoneal space	Transudate/exudate Sometimes chylothorax
Thoracic duct injury	Chylothorax
Vascular rupture	Haemothorax

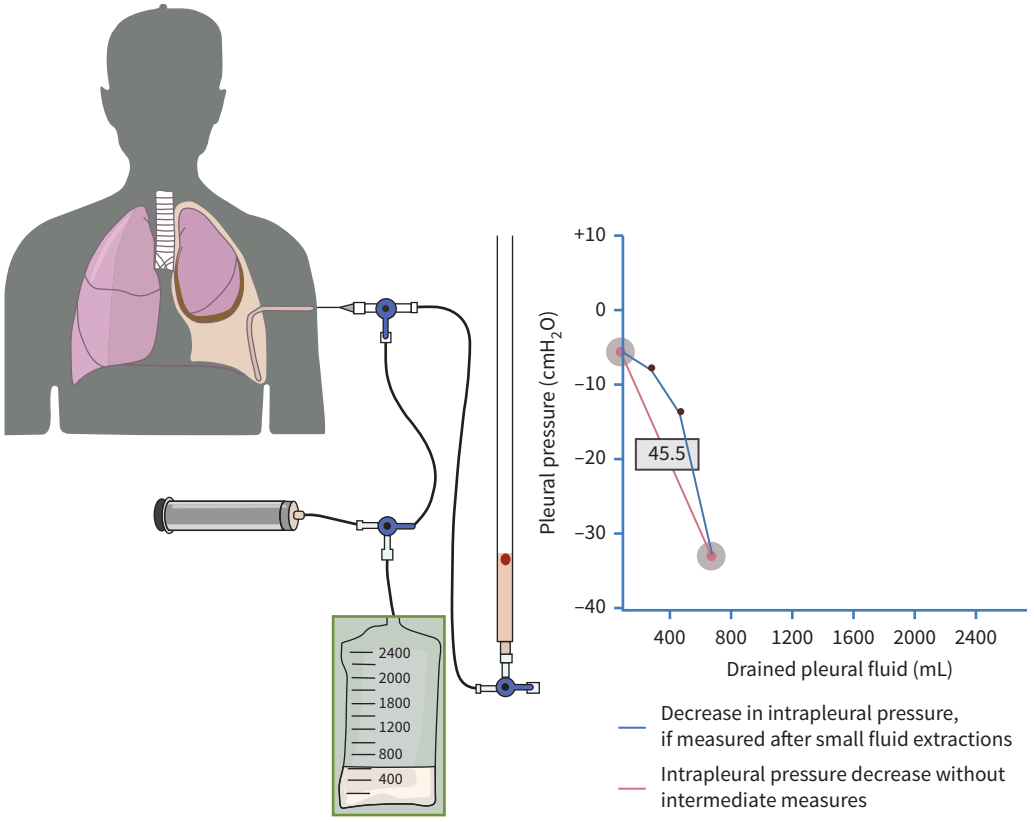

FIGURE 2 In the trapped lung, the visceral pleura has a thicker layer of fibrin, due to a previous disease, which will prevent lung re-expansion. For this reason, the initial pleural pressure will be negative. The withdrawal of fluid, on one hand, and the stiffness of the lung, on the other, will cause a rapid decrease in pleural pressure, leading to elevated pleural elastance. Pleural elastance=45.5, which is the difference between the initial intrapleural pressure and the final intrapleural pressure after withdrawal of 600 mL, either in a single extraction (red line) or after three consecutive extractions (blue line). Modified from [4] with permission of the Spanish Society of Pulmonology and Thoracic Surgery.

abdominal cavity. Thus, hepatic hydrothorax [46] and urinothorax [47] are generally a transudate, whereas pancreatitis [48] and Meigs syndrome [49] are usually exudates. This would be the most frequent mechanism of PE of subdiaphragmatic origin, although it may also result from communication between the two cavities, such as in the case of fistulas [50].

Thoracic duct rupture

Traumatic rupture of the thoracic duct, whether surgical or not, causes chylothorax, which shares the characteristics of the PE described in the previous section. In these cases, chyle leak output is higher, leading to greater morbidity and mortality. Early detection is crucial, since it may require urgent surgery to preserve the patient's life [43].

Vascular rupture

Haemothorax, the entry of blood into the pleural space, may result from thoracic, lacerating or penetrating trauma, iatrogenic procedures of various kinds or non-traumatic diseases, including spontaneous haemopneumothorax. In haemothorax, bleeding is usually caused by the shearing of the adhesions between the two pleurae. The presence of pneumothorax prevents lung tamponade while blood is accumulating in the pleural space under a systemic pressure that is approximately six times greater than in the pulmonary arterial circulation [51]. Diagnosis is established on the basis of a PF/serum haematocrit ratio >50% [31].

Types of PE

In clinical practice, transudates are separated from exudates by measuring the amount of a given solute in the pleural space. There is evidence that the concentration of a solute in PF is solely determined by its

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TABLE 2 Diagnosis of certainty, or of high diagnostic probability, of a pleural effusion established through the pleural fluid analysis or the pleural fluid/serum ratio, as well as the mechanisms by which it occurs

Parameter (in PF, unless otherwise specified)	Diagnostic characteristics	Most likely diagnosis	Pathophysiology
Adenosine deaminase	>45 $U \cdot L^{-1}$ and lymphocytes >50%	Tuberculosis	Rupture of a subpleural caseous focus and mycobacterial antigens interact with $CD4^+$ T-lymphocytes producing a hypersensitivity reaction It is released by macrophages stimulated by the living microorganisms inside them
Amylase PF/serum	>2	Acute pancreatitis	Acute inflammation of the pancreas produces an exudative fluid that is transferred through interconnected lymphatic vessels on both sides of the diaphragm into the pleural space
Amylase	>100 000 $U \cdot L^{-1}$	Pleuro-pancreatic fistula	Due to obstruction of the pancreatic duct
β_2 transferrin	Present in PF	Duropleural fistula	Communication between the subarachnoid space (positive pressure) and the pleural space (negative pressure) The cerebrospinal fluid flows through a pressure gradient from the space with the highest pressure to the one with the lowest pressure
Bilirubin PF/serum	>1 (greenish appearance)	Biliopleural fistula	Complete biliary obstruction or prolonged drainage (>7 days) favours fistula formation
C-reactive protein	⩾100 $mg \cdot L^{-1}$ and neutrophils >50%	Pleural infection	Acute phase reactant released by the liver that is elevated as a nonspecific response to infection and non-infectious inflammatory situations PE is produced by increased pleural capillary permeability
Cholesterol	⩾250 $mg \cdot dL^{-1}$	Pseudochylothorax	A pleural thickening blocks the drainage of PF to the lymphatic system; the lysis of red blood cells and neutrophils trapped in the pleural space causes an increase in cholesterol released in the PF
Creatinine PF/serum	>1 (colour and smell of urine)	Urinothorax	Obstructive urinary disease with urine passing from the abdominal or retroperitoneal cavity to the pleural space due to a pressure gradient
Culture	Positive	Pleural infection	Presence of the microorganism in pleural fluid
Cytology	Positive	Neoplasia	Implantation of the tumour in the subserous layer
Glucose PF/serum	>1 (if a glucose solution received) and anomalous position of the catheter	Extravascular migration of the central venous catheter	Erosion of the superior vena cava due to a catheter of insufficient length
Haematocrit PF/serum	>0.5	Haemothorax	Presence of blood in the pleural space
Interferon-γ	>140 $pg \cdot mL^{-1}$	Tuberculosis	Rupture of a subpleural caseous focus and mycobacterial antigens interact with $CD4^+$ T-lymphocytes producing a hypersensitivity reaction Cytokine released by $CD4^+$ T-lymphocytes to increase the mycobactericidal activity of macrophages
LE cells	Positive	SLE	Localised immune inflammation process with activation of the complement system and production of immunocomplexes
Löwenstein culture	Positive	Tuberculosis	Presence of *Mycobacterium tuberculosis* in PF
Mesothelin serum	>2.00 $nmol \cdot L^{-1}$	Malignant pleural mesothelioma	Implantation of the tumour in the subserous layer Mesothelin is expressed in normal mesothelial cells and overexpressed in mesothelioma, lung, ovarian and pancreatic cancer
NT-proBNP	⩾1500 $pg \cdot mL^{-1}$	Heart failure	Molecule secreted by the cardiac ventricles in response to their acute distension
Total proteins	<1 $g \cdot dL^{-1}$	Peritoneal dialysis	Dialysate may migrate from the peritoneal cavity to the pleural space through a pleuroperitoneal leak
Triglycerides	⩾110 $mg \cdot dL^{-1}$	Chylothorax	Obstruction/rupture of the thoracic duct causes lymph to accumulate retrogradely in the pleural space
Tumour markers (*e.g.* carcinoembryonic antigen)	Elevated	Neoplasia	Tumour cells implanted in the pleura can express a greater amount of a certain protein in PF The marker varies depending on the type of tumour

PF: pleural fluid; PE: pleural effusion; LE: lupus erythematosus; SLE: systemic lupus erythematosus; NT-proBNP: N-terminal pro-brain natriuretic peptide.

concentration in blood and the permeability of the pleural capillaries. Hence, a solute concentration is not determined by the amount of solute extravasated by the leukocytes and erythrocytes into the pleural space after solute degeneration [52]. Therefore, exudates should contain higher concentrations of any solute than transudates [53, 54]. So far, no single parameter has been found to be superior to the others in separating transudates from exudates [55], especially considering that their concentration in PF may be influenced by different factors [56]. Although it is out of the scope of this review, it is necessary to determine which parameter differentiates exudates from transudates most effectively. Ideally, the most effective parameter would be one with such a high molecular weight that, in the absence of an increased vascular permeability, filtration through the endothelium of the pleural capillaries was difficult.

When performing a differential diagnosis and investigating the aetiology of a PE, whether a transudate, exudate, chylothorax or haemothorax, it is essential to be familiar with the predominant underlying pathophysiological mechanisms that cause the accumulation of fluid in the pleural space. Cellular mechanisms are of special interest, as their inflammatory and immunological reactions are reflected in the composition of PF and pleural tissue. Therefore, interpreting correctly the information obtained from the analysis of PF and pleural tissue is essential. Although it is not the aim of this review, measurement parameters such as pH, glucose, C-reactive protein, adenosine deaminase, interleukins, carcinoembryonic antigen and soluble urokinase plasminogen activator receptor (suPAR), to name a few, in PF may be useful for the differential diagnosis of PE and determine the need for invasive diagnostic or therapeutic procedures [57–59]. Table 2 shows the certain (or high probability) diagnoses that can be established by PF analysis and the pathophysiological mechanism involved [4, 30, 31, 58, 60, 61].

On another note, there are some considerations to be taken into account. Firstly, abnormal PF collections occur as a result of an insult to the pleura, which reacts differently according to the type of insult. The different PE etiologies are associated with different response patterns, with PF having specific analytical characteristics. However, a prospective study revealed that pleural response is heterogeneous, and the pleura may respond differently to the same aetiology or similarly to different etiologies, which makes diagnosis of PE difficult [62]. Secondly, in 30% of cases, PE is caused by several underlying diseases, with different mechanisms being simultaneously involved. Identifying these mechanisms may be crucial to determining the best therapeutic approach and ensuring clinical benefit [63]. Finally, PF may change biochemically over time. In the early stages of some malignant PEs, fluid may begin to accumulate due to lymphatic drainage obstruction rather than to direct infiltration through the pleura [64]. At that point, the fluid would behave as a transudate; the reason is that PF would be an ultrafiltrate of plasma with a low protein content, requiring several weeks for the accumulated protein to exceed 50% of serum concentration [65]; this would cause a non-negligible percentage of malignant PEs to behave biochemically as a transudate [66].

In summary, under physiological conditions, the fluid in the pleural space, which couples the lung to the rib cage, is constantly changing and maintains equilibrium between fluid inflow and outflow. Different pathophysiological mechanisms can lead to the accumulation of fluid in the pleural space. These mechanisms are activated by inflammatory and immunological reactions that take place in the mesothelial cells and the pleural space in response to a given insult (disease). For clinicians to understand the heterogeneity of pleural response and identify the aetiology of PE, it is necessary to be aware of the physiology and pathophysiology of PF movements and correctly interpret analytical findings in PF and pleural tissue.

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