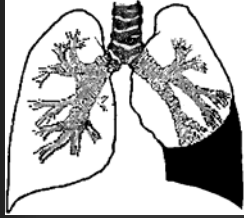


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How Pleural Effusion Causes Dyspnea?

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The sensation of breathlessness is a common symptom accompanying pulmonary and cardiovascular disease. Dyspnea in patients with a pleural effusion may be due to the underlying cause of the effusion such as congestive heart failure, due to an unrelated condition, or due to the pleural effusion itself. Clinically, the cause of dyspnea is attributed to a pleural effusion if relief after drainage can be demonstrated. Although clinical experience confirms that pleural effusion in itself can cause dyspnea, the physiologic mechanisms by which the sensation is produced are considerably more difficult to demonstrate.

Dramatic relief of dyspnea after thoracentesis may be seen in subjects with only small increases of functional parameters as measured by pulmonary function testing. Likewise, gas exchange abnormalities do not explain the degree of dyspnea in most patients. However, as Estenne and colleagues have demonstrated, the decrease of intrathoracic volume after thoracentesis exceeds by a factor of two the increase in TLC.

A pleural effusion does not uniformly increase intrathoracic volume as a pneumothorax would, but rather collects over the diaphragm and may compromise its function more than the volume change alone would suggest.

The change of the intrathoracic volume may be calculated by: Lung Volume pre-thoracentesis + Effusion Volume – Lung volume post-thoracentesis (for RV, FRC, TLC). The decrease in size of the ribcage and restoration of the dome shape of the diaphragm increases the inspiratory muscle length at end-expiration and improves contractile efficiency in relation to the neural input. In other words, the presence of a pleural effusion leads to a decreased (afferent) mechanoreceptor input for a given (efferent) motor output, giving rise to the sensation of dyspnea. Of interest, this model does not require, but also does not exclude, afferences originating in the lung.

Obviously, additional considerations apply in patients with very large effusions, which may interfere with gas exchange, venous return, and may even result in subtle cardiac tamponade physiology.

In summary, the effects of a pleural effusion on the neuromuscular system and the ventilatory pump remain the most likely mechanism by which the sensation of dyspnea is created. Moderate pleural effusion thus represents a space occupying lesion in the chest with direct mechanical effects on the mechanism responsible for ventilation. The model does not require humoral mediation which, in any case, would fail to explain the relief of dyspnea after thoracentesis in patients at rest with normal blood gas values, a finding commonly encountered in clinical practice.

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permeability of the capillary endothelium to water and protein² which are indicated by the filtration coefficient, K_f , and the osmotic reflection coefficient, σ , respectively:

$$F = K_f \cdot [(P_{cap} - P_{pl}) - \sigma (\pi_{cap} - \pi_{pl})].$$

The capillaries of the parietal pleura originate from systemic vessels so the hydrostatic pressure within them mirrors that of other systemic capillaries, i.e. about 25 mmHg. Intrapleural pressure is slightly subatmospheric (about -3 mmHg), so the hydrostatic gradient favors fluid formation. This gradient is partially offset by the oncotic pressure gradient resulting from the higher protein concentration in plasma ($\pi_{cap} = 28$ mmHg) than pleural fluid ($\pi_{pl} = 5$ mmHg). The reflection coefficient for the pleural capillaries is about 0.9, so the effective oncotic pressure difference opposing fluid efflux is $0.9 \times (28 \text{ mmHg} - 5 \text{ mmHg}) = 21$ mmHg. Thus, the balance of hydrostatic and oncotic pressures favors fluid filtration from parietal capillaries into the pleural space.

There are two potential routes for pleural fluid reabsorption: the capillaries of the visceral pleura and the lymphatics within the parietal pleura that drain the pleural cavity. The visceral pleural capillaries are derived from bronchial arteries (systemic vessels) but drain into pulmonary veins³, so the hydrostatic pressure within these capillaries is probably similar to that within pulmonary capillaries (about 10 mmHg). Fluid reabsorption would be favored under physiologic conditions but these microvessels would be an additional site of fluid efflux in the patient with left heart failure.

However, under physiological conditions, the lymphatics of the parietal pleura are the most important route for fluid reabsorption. Although the visceral pleural capillaries may reabsorb water, they are relatively impermeable to protein and the pleural fluid protein concentration would increase as fluid is reabsorbed via this route, reducing the oncotic gradient opposing fluid filtration. The lymphatic removal of fluid and protein is essential to maintain a normal oncotic gradient across the pleural membranes. Quantitatively, lymphatic flow appears to be responsible for most of the fluid efflux and virtually all protein reabsorption from the pleural cavity under physiologic conditions^{4,5}.

Effusions are classified as transudates or exudates based on the protein and lactate dehydrogenase concentrations in the fluid. The protein concentration of a transudate is low because the pleural capillary endothelium is intact and its ability to retain plasma proteins within the vascular compartment is preserved. The development of an exudative effusion implies a loss of integrity of the pleural membrane and/or disruption of the normal lymphatic clearance mechanisms. The physiologic derangements are more severe and management is often more difficult.

Mechanism of Pleural Effusion Formation

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Effusions accumulate whenever the rate of pleural fluid formation exceeds that of its reabsorption. The parietal and visceral pleural membranes are normally separated by a thin (10-30 μ m) layer of fluid that is formed as an ultrafiltrate from the capillaries beneath the mesothelium.

The mesothelium of the pleura is extremely permeable and offers little resistance to water and protein movement¹. Fluid flux (F) between submesothelial capillaries and the pleural space is determined by the distribution of hydrostatic (P) and oncotic (π) pressures within the capillaries (cap) and pleural space (pl), and the

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Composition of Normal Pleural Fluid

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The pleural space in normal humans contains a small amount of fluid. This fluid is thought to “lubricate” the visceral and parietal pleural surfaces, thus enabling transmission of the forces of breathing between the chest wall and the lung. The amount and composition of this fluid reflect the balance between continuous dynamic phenomena involving the pulmonary and systemic circulation, hydrostatic and oncotic pressures, lymphatic drainage, the mechanical action of the thoracic cage, and the movement of the heart¹.

The volume and cellular and solute content of the normal pleural fluid in humans have long remained one of the last “Schrödinger’s cats” of body fluid composition. This is because, somewhat in analogy with Schrödinger’s paradox, invasive measurements in normal pleural spaces invariably caused a major disturbance of the system.

Until recently, only a few animal experiments and one human study (from 1933!) were available². In 2000, we published our results of volume and cellular content measurements using the indirect technique of pleural lavage through thoracoscopy, performed in normal humans undergoing thoracoscopy for treatment of sympathetic disorders³. We injected 150 ml of pre-warmed saline into the pleural cavity, immediately after induction of a pneumothorax. After a minimal dwell time of a few seconds, the total fluid (that is, the injected volume of saline mixed with the

originally present small volume of normal pleural fluid) was aspirated, and processed. With urea used as an endogenous marker of dilution, mean right-sided pleural volume in young, healthy subjects, was 8.4 +/- 4.3 mL. In a subgroup of patients we showed that left- and right-sided volumes were similar. Expressed per kg bodyweight, total right + left sided pleural fluid volume in normal, non-smoking humans was 0.26 +/- 0.1 mL/kg, which corresponds very well with the volume of 0.3 mL/kg as extrapolated from animal studies⁴.

Taking into account the dilution factor caused by the saline instillation, the total white blood cell count in the original pleural fluid was 1,716 x 10³ cells/mL. Differential cell counts were: macrophages (median 75%), lymphocytes (median 23%), and sporadic eosinophils, neutrophils and mesothelial cells. Interestingly, a small but significant increase in neutrophils was observed in normal smokers.

Normal pleural fluid contains 1-2 g of protein per 100 mL, which is similar to interstitial fluids⁵. Levels of large molecular weight proteins, such as lactate dehydrogenase, are less than half of that found in the serum.

In summary, normal human pleural spaces contain a small amount of liquid (0.26 +/- 0.1 mL/kg body weight) with biochemical characteristics of interstitial fluid. It contains a fair amount of white blood cells (and a few red blood cells), which consist mainly of macrophages (75%) and lymphocytes (25%).

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If you have any comment on the Newsletter or any interesting cases of pleural disease, contact:

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IMAGES OF THE PLEURA

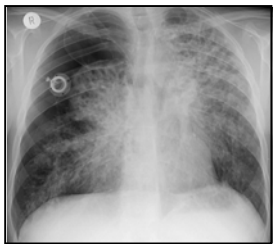
Pleural Complications in Adults with Cystic Fibrosis

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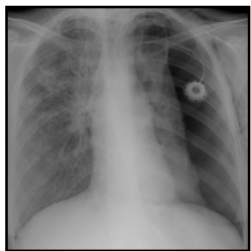
Pleural complications are common in cystic fibrosis (CF). Among these, pneumothoraces are the most frequently encountered although their pathogenesis remains incompletely understood. Surprisingly, pleural empyema in non-transplanted CF patients has rarely been reported. Occasionally, bacterial infection may complicate pneumothoraces. We report three cases of CF pleural complications, highlighting key clinical features and discuss their central management points.

Patient 1. A 23-year-old male CF patient with allergic bronchopulmonary aspergillosis (ABPA) and chronic



Stenotrophomonas maltophilia colonization presented with severe acute dyspnea. Plain radiography demonstrated a right-sided trachea-displacing pneumothorax that was partly obscured by a large apical bulla. This was his 3rd

ipsilateral pneumothorax within a six-month period. As on previous occasions, chest tube drainage was deployed successfully without recourse to surgery. However, several months later, the patient developed two left-sided pneumothoraces that required surgical intervention. The bullae, including the solitary right-sided defect, were left unexcised.

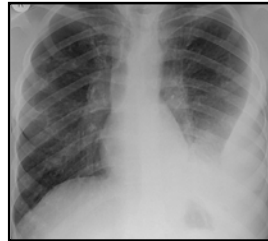


Patient 2. A 23-year-old female CF patient with ABPA, bilateral apical bullae and a previous surgically-treated right-sided pneumothorax presented with acute breathlessness, chest pain and radiographic evidence of a complete left-sided

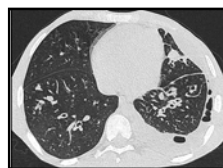
pneumothorax. Insertion of a chest tube led to a prolonged and futile attempt to re-expand the lung. She eventually received surgical bullectomy and abrasion. *Candida albicans* was cultured from bronchoalveolar lavage fluid that was sampled during the operative procedure. Post-operatively, she developed a persistent air leak and a pronounced systemic inflammatory response. *C. albicans* was simultaneously isolated from blood, urine and sputum. The same organism, as well as *Aspergillus*, was

present in pleural fluid drained. The patient was treated with a prolonged course of voriconazole and made a slow but steady recovery over the subsequent two months.

Patient 3. A 22-year-old male was admitted with an infective exacerbation of his CF. His disease was complicated by chronic *Pseudomonas aeruginosa* and *Staphylococcus aureus* colonization, marked pancreatic insufficiency and intermittent rectal prolapse. The presence of a fever, leukocytosis and raised C-reactive protein (62mg/L) were noted. Plain radiology showed opacification of the left lower zone. CT scanning revealed compressive atelectasis



of bronchiectatic lung, and a pleural collection containing



loculated air that proved to be an empyema at diagnostic sampling. Failure of clinical and radiologic resolution after a week of parenteral antibiotics necessitated pleural decortication attained via muscle-sparing thoracotomy. No micro-organisms were isolated from the pleural contents.

Discussion: As the median age of survival for CF patients has increased over the past two decades, a greater number of pleural complications is expected to occur in adults with the condition. A 1% annual incidence of pneumothorax has been quoted by the Cystic Fibrosis Foundation Registry database¹. Risk factors that confer a greater likelihood of developing pneumothoraces include FEV₁ <30% predicted, presence of *Pseudomonas aeruginosa*, *Burkholderia cepacia* or *Aspergillus*, concurrent ABPA and the use of enteral feeding². In the current report, patients 1 and 2 had an FEV₁ of sub-30% predicted. Despite the suppurative nature of CF, bacterial empyema in non-transplanted adult CF patients has only rarely been reported in the literature³. Failure to identify a causative organism is not surprising, given the high likelihood of chronic antibacterial use in this population of patients. Nevertheless, it is vital that pleural empyema is promptly diagnosed since a combined surgical and medical management may be required to achieve a successful resolution.

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