Chapter 5
Extravascular Lung Water Monitoring

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5.1 Definition and a Brief History

Water contributes 80% of the lung components; however, most of them existed in the blood vessels and distributed in a gradient of increasing density from nondependent to dependent regions. By definition, extravascular lung water (EVLW) is the amount of water that is contained in the lungs outside the pulmonary vasculature, composed of the sum of interstitial, intracellular, alveolar, and lymphatic fluid; however, pleural effusions did not include [1]. The EVLW monitoring and evaluation play an essential role in pulmonary edema assessment.

5.2 Physiology of Lung Water

In human beings, about 700 million alveoli are contained in both lungs, with an overall surface area of approximately 100 m². The alveoli consist of an epithelial layer, interstitium, and capillaries. The lungs work in a unique engineering fashion since air circulates in the alveoli, while blood circulates in capillary surrounded outside. The extravasation of fluid and solutes from the pulmonary microvessels into the pulmonary interstitial tissue is a physiological phenomenon, which is usually constrained in the interstitium, with little possibility to reach the alveoli due to the intact junctions of the alveolar epithelium. The process of fluid movement across the barrier between pulmonary capillaries and interstitial spaces is determined with the gradient of hydrostatic and oncotic pressure, as well as the filtration coefficient.

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of the alveolocapillary barrier, all of which bundled together and known as the Starling’s law (Fig. 5.1), which is proposed by Ernest Starling as early as 1896 [2].

The doctrine status of the Starling model has been challenged for a long time. Danielli found there was an endothelial surface layer lining the luminal side of the capillary endothelium in 1940 [3]. Recent studies found a nonlinear relationship between hydrostatic pressure and vascular permeability [4, 5]. Endothelial glycocalyx (EG), which composed of glycosaminoglycans and proteins and coating the surface of endothelial-like a gel, is believed to play a crucial role in extravasation prevention [6]. Acting as a molecular sieve, EG can limit water and solute efflux across the intercellular junction. Furthermore, EG provides scaffolding on which serum plasma proteins accumulate and a layer of ultrafiltrate formed, which pulls fluid to the intravascular compartment with the powerful oncotic force. Additionally, EG transmitting the shear stress from blood flow to the endothelium cytoskeleton and initiating intracellular signaling as a mechanosensor, increasing capillary permeability [7].
The understanding of the pathophysiology of pulmonary edema goes further based on the emerging role of EG. It is well acknowledged now that excessive fluid extravasation could be induced by either a significant increase of capillary hydrostatic pressure or the damage of the EG layer, which is frequently seen in trauma and ischemia/reperfusion injuries.

The pulmonary lymphatics serve as a drainage system, which presents along the peribronchovascular, interlobular septa, and the pleural spaces are responsible for EVLW clearance by actively removing fluid and solutes from the interstitial tissue and poured into the superior vena cava through the thoracic duct continuously. Zarins demonstrated that the lymph flow is about 20 mL/h normally and could increase 5–10 times to compensate for the increase of interstitial pressure [8]. Gee reported that when transpulmonary pressure was increased to 20 cmH₂O, water content contained by the peribronchovascular cuffs increased by 70% [9]. Further extravasation of interstitial fluid is limited due to the progressive decrease of the interstitial compartment compliance. This protection could be destroyed due to the breakdown of interstitial proteoglycans, which caused loss of matrix integrity.

The dynamic equilibrium between the fluid leakage and lymphatic drainage is essential to maintain the dryness of the lungs, and hence preserve the normal function of oxygenation.

In terms of the movement of extravasated fluid into the alveoli from the interstitium, the process is quite faster. The mechanisms of alveolar fluid clearance (AFC) is responsible for the removal of excess fluid from the alveoli to the interstitial tissue across the alveolar epithelial barrier, in which the active ion transport plays a key role. The sodium permeant ion channels expressed in the distal lung epithelium are responsible for actively transport sodium back into the interstitial space, with chlorine and water following. Other molecular transporters including but not limiting the cystic fibrosis transmembrane conductance regulator, Na⁺-K⁺-ATPase, and several aquaporin water channels. The process of isosmolar fluid transport across the distal lung epithelium is upregulated by both catecholamine-dependent and -independent mechanisms [10].

The AFC rate depends on the species difference. In human beings, roughly on the order of 25% per hour [11], whereas in mice may be as high as 50% per hour [12].

Regulated with the mechanisms described above, EVLW seldom exceeds 500 ml in normal lungs; however, it may be 75–100% higher in the condition of alveolar flooding. Typically, increased interstitial EVLW is caused by increased hydrostatic pressure in the pulmonary capillaries (as occurs in congestive heart failure), decreased oncotic pressure (such as hypoalbuminemia), or the increased permeability of the alveolocapillary barrier (as in the ARDS) [13]. The accumulation of EVLW in interstitial spaces will thicken the blood-air barrier (0.5–2 μm in the normal range), impede the gas exchange under the same alveolar-arterial difference of oxygen, and reduce lung compliance.

It is well known that one of the major pathophysiological characteristics of ARDS is the increase of pulmonary permeability and the increase of hydrostatic pressure also prevalent due to fluid resuscitation. In the early phase of ARDS, the increase in interstitial EVLW could be compensated by the enhancement of lymphatic drainage. Once the speed of drainage is overwhelmed by high filtration rate and fluid enters the alveoli, the impaired active ion transport and lymphatic drainage
network may not clear excess fluid effectively, leading to the accumulation of EVLW, and what is worse is the flood of alveoli. Apart from ARDS, an increase of EVLW is also seen in septic shock [14] and other critically ill patients.

Indexed to the body weight (mL/kg), instead of absolute value (ml), EVLWI is better correlated with the oxygenation and the lung injury score, provide more accurate information in predicting the mortality of patients with ARDS. After screening a series of autopsies in Japan from more than 800 hospitals between 2004 and 2009, Tagami and colleagues compared the postmortem lung weights, and converted to EVLW with the following equation [15]:

$$\text{EVLW} (\text{mL}) = [0.56 \times \text{lung weight (g)}] - 58.0.$$

Their results showed the mean value of EVLWI was 7.3 ± 2.8 mL/kg in 534 normal lungs, and 13.7 ± 4.5 mL/kg in 1688 lungs with diffuse alveolar damage (DAD), respectively. The cut-off value higher than 10 mL/kg could establish the diagnosis of DAD with a sensitivity of 81.3% and a specificity of 81.2%, therefore lower than 10 mL/kg is regarded as the normal values of EVLWI.

It will be a great value to detect and quantify the EVLW in monitoring the progression of the illness, evaluating the severity, and accessing treatment response accurately and timely. The histologic and gravimetric methods are good for experimental study; however, they could not be used in the clinical scenario. Ideally, a technique that fulfills the advantage of noninvasive, easy to implement, reproducible, and less expensive concomitantly is preferred by clinicians, which may provide enough information with sufficient sensitivity and specificity.

5.3 The Methods of EVLW Measuring

5.3.1 Gravimetry

Gravimetry remains as the golden standard in EVLW measuring. It is a precisely laboratory postmortem technique, which measures the total lung water by weighting the difference of lungs before and after desiccation. The amount of intravascular lung water could be estimated by comparing the hematocrit in systemic blood and lung specimen, assuming red blood cells do not cross the alveolar-capillary barrier, although it is not always true. Subtracting intravascular lung water from total lung water, we could know the EVLW.

5.3.2 Imaging Methods

The information provided by all imaging methods is spatially related, which means that each pixel (picture) or voxel (volume) in a cross-sectional image of the lung corresponding to a specific physical volume. Different from other solid organs, the
lung is air-containing and the parenchyma in a specific region varies with the state of lung inflation. The signal must be integrated over the entire lung to quantify changes in images of EVLW.

It has to be pointed out that imaging methods (except for positron emission tomography) just provide a rough estimation of total water content or concentration, and could neither differentiate extravascular water from vascular water technically, nor extracellular from intracellular water. If the blood volume varies with the hemodynamic status, the data calculated from imaging methods may mislead the estimation of EVLW.

5.3.3 Chest Radiography

Conventional chest roentgenogram is fast and easy to acquire method for detecting the presence of pulmonary edema, describing the overall distribution with the lung, and semi-quantifying the amount of exudate fluid. The typical signs such as pulmonary “congestion,” vascular “redistribution,” peribronchial cuffing, perihilar “haze,” septal (Kerley) lines, and “interstitial” pattern to the radiographic densities may indicate the modest increases in EVLW (more than 35%) [16]. Further increase of EVLW presents with acinar opacities, ground-glass opacities, and frank consolidations. Initially, the distribution of increased radiographic density may be prominent regionally, i.e., gravity-dependent lung regions, and even turned to be opacity with the progression of fluid exudation.

In the clinical environment, the degree of interobserver variability and the lack of sensitivity raised concerns about the accuracy of chest radiography monitoring. For example, the interobserver variability ranged from 36% to 71% in diagnosing ARDS based on the American-European Consensus Conference definition, after reviewing 28 chest radiographs by 21 radiology experts [17]. Compared with CT, the accuracy of chest radiography was only 72% in alveolar-interstitial pulmonary edema assessment [18].

Apart from the limitations mentioned above, sometimes the X-rays are difficult to interpret, which is often the case in supine ICU patients, influenced by the heart and relaxed diaphragm. Besides, repeated radiation exposure brings safety risks to chest X-ray photography, all of which require the use of more sensitive and accurate techniques when evaluating EVLW.

5.3.4 Computed Tomography

Computed tomography (CT) enables the visualization of lung lesions from the apex to the bottom, from the anterior to the posterior regions, and quantify the infiltrate density of the lungs. In transverse sections of CT display, the arbitrary Hounsfield units (HU) calibrated against substances of known density, could easily define the spatial distribution of edema. Normally the value of 0 HU characterizes a voxel with
a density equal to that of water and the value of −1000 HU characterizes a voxel with a density equal to that of air. In isolated canine lungs, CT densitometry can detect modest increases in EVLW [19].

The disadvantages of CT include exposure to large doses of ionizing radiation (i.e., pregnant women or preterm infants), time-consuming, unrepeatable, and facing the risk of critically ill patient’s transportation. Different from the previous studies, the most recent study questioned the diagnostic value of quantitative CT analysis for the assessment of pulmonary fluid status in unselected critically ill patients, mainly contribute to the real clinical routine other than a standardized protocol, i.e., without an end-expiratory pause while receiving mechanical ventilation [20].

5.3.5 Lung Ultrasonography

Although echocardiography is widely used in the ICU, the lung was not considered suitable for this imaging technology for a long time. Clinicians started the exploration of lung ultrasound since 1989 and gradually turned it to be a valuable point-of-care (POC) tool in the assessment of acute pulmonary diseases [21]. Healthy lung tissue is poorly penetrated by ultrasound due to the high acoustic impedance of air, which is usually defined as “black” lung. However, in the condition of increased EVLW, the air-fluid interface between collapsed, fluid-filled, and aerated alveoli will result in the acoustic reverberation artifacts, which provide the possibility of transmission of ultrasound deep into the diseased lung tissues.

With multimodal scanning of the anterior and lateral lung at different locations with 5–13 MHz linear array or 1–6 MHz phased array ultrasound probes, a panoramic impression of the complete lung and pleura could be achieved. B-lines (also named lung rockets) are well-defined, hyperechoic artifacts arising from the pleural line fanning down into the far-field of the screen without fading will display more than three in the condition of increased EVLW. In severe pulmonary edema, more B-lines are seen in narrow distance apart, and merge to display ground-glass rockets, also called “white lung.” The linear correlation between the quantity of B-lines and the amount of EVLW is well acknowledged and make it possible to a semi-quantitative estimation of EVLW by counting the number of B-lines (Fig. 5.2).

Lung ultrasonography has high sensitivities and specificities in detecting EVLW when compared with other methodologies such as chest radiology, CT, or transpulmonary thermodilution. Combined with advantages of economic, fast, immediate, and dynamic feedback, free of radiation exposure, lung ultrasonography is very useful in daily clinical fluid management. Of course, standardized training is essential to limit the variation of the practitioner.
5.3.6 Nuclear Magnetic Resonance Imaging (MRI)

The principles of using MRI in evaluating EVLW are based on the fact that the signal of any MR image is related to the number of protons present. Under the external magnetic field, the hydrogen nuclei (protons) of water will align and keep in the same direction. Resonance comes from absorption and subsequent release of energy when the subject is irradiated with electromagnetic radiation in the form of a certain radiofrequency pulse, which is applied and discontinued regularly.

Although the lung is difficult to image since the overall density is low and subsequently MR signal is weak, early studies in excised animal lungs have demonstrated excellent correlations between gravimetric and MRI water content [22, 23]. However, it is impractical to use in the human examination due to long imaging
times of T2-decay (>6 min per slice) [24], since it should be completed within a single breath-hold.

The development of rapid imaging techniques such as submillisecond echo time (TE) gradient echo (GRE) imaging makes it possible to measure the proton density of the lung in a single breath-hold [25]. Theilmann et al. adapted GRE sequence to collect 12 images alternating between two closely spaced echoes in a single 9-s breath-hold, and the resulting data were fit with a single exponential decay function to determine T2* and lung water by back-extrapolating signal to an echo time of zero [26]. Albeit absolute values may be overestimated a little bit (errors are systematic and less than 10%, ~10 g), this technique has been proved reliable and valid compared with the ex vivo gravimetric method, regardless of lung volume or density, which enables the assessment of lung water content in a single breath-hold, and thus may offer significant advantages in the study of human lung disease and physiology [27].

5.3.7 Indicator Dilution Methods

5.3.7.1 Transpulmonary Thermo-Dye Dilution

When injected via central venous, freely diffusible (heat/cold) and a non-diffusible (indocyanine green dye which binds to albumin) indicator each have the same flow but through different volumes of distribution. The difference in the mean transit times of the two indicators is, therefore, extravascular thermal volume (ETV). Since compared with the extravascular water content of the lung, the extravascular water content of myocardium and non-pulmonary blood vessels is small, ETV and EVLW are usually considered to be equivalent.

Lewis introduced the thermos-green dye dilution technique in the early 1980 [28] and validated against gravimetry in human beings [29]. In detail, 10 mL of cold (0 °C) indocyanine green dye (4 mg) is injected rapidly into superior vena cava through a central catheter, then withdrawn by syringe pump through a densitometer cuvette attached to the femoral catheter with the speed of 30 mL/min, and recorded the curves of both the thermodilution and dye concentration versus time. The collected data is processed by the computer and EVLW is derived from the difference between the volume of distribution of the indicator diffusing into the extravascular space (cold) and of the green dye remaining in the circulation. As the double indicator dilution technique, thermos-dye dilution has been replaced by the single indicator thermodilution technique and is not available in the market anymore.

5.3.7.2 Transpulmonary Thermodilution (TPTD)

TPTD uses a cold indicator delivered into a central vein and detected by a thermistor tipped catheter in the aorta (either in the femoral or axillary artery), resulting in the recording of a thermodilution curve. During pulmonary transit, the presence of
pulmonary edema will result in the indicator loss by warming the fluid bolus, and this loss of indicator is used to quantify EVLW. The application of TPTD is based on the assumption that the pulmonary blood volume represents 20% of the intrathoracic blood volume (ITBV), or 25% of the global end-diastolic volume (GEDV), which comes from the observations reported by Sakka et al. in 2000 [30]. Due to the individual variability between pulmonary blood volume and ITBV, TPTD is only the best estimation, instead of a precise measure of EVLW [31].

Compelling evidence showed the power of TPTD in early and accurate measuring EVLW. In a porcine model of hydrostatic pulmonary edema conducted by Bongard, a strong linear association exist between ELVW and increase in perivascular cuff width to vessel diameter ratio, interalveolar septal width, and alveolar flooding, and 100% increase of EVLW is required before the onset of hypoxemia or histologic changes [32]. In another porcine study, researchers demonstrated that TPTD could detect a modest increase of EVLW, even only 50 mL of saline is instilled into the trachea [33]. In terms of reliability, the coefficient of variation of EVLW ranging from 4.8 to 8% suggests it is highly reliable [34]. In the case report of ARDS induced by 2009 pandemic influenza A (H1N1) virus, the maximum of EVLW once reached 33 mL/kg, coincidence with poor respiratory compliance and low PaO₂/FiO₂ ratio, and decreased with the improvement of clinical symptoms and respiratory parameters, showing its high value of monitoring EVLW dynamically [35].

Since the central venous and arterial cannulation are common in ICU, TPTD monitoring is easy to perform. By measuring the cardiac preload concomitantly, it is possible to differentiate increased capillary permeability from the increased hydrostatic pressure, which is typically seen in ARDS and cardiac failure, respectively. It must be pointed out that the TPTD only measures lung water in perfused areas of lung and therefore rely on the homogenous distribution of pulmonary perfusion. Mismatch of ventilation-perfusion will lead to errors in the estimation of EVLW, e.g., pulmonary embolism, lung resection, and high level of positive end-expiratory pressure.

Until now, TPTD is the only methodology available at the bedside to evaluate the amount of EVLW, with the advantage of nonoperator dependent, nurse-performed, and helpful in differentiating the etiology of pulmonary edema. However, the relatively high cost and invasive nature limit its widespread use.

### 5.4 Conclusion

Assessment of lung water is crucial in pulmonary edema diagnosis and management. Several methodologies are available to quantify lung water, depending not only on the understanding of the unique advantages and limitations of these approaches but also the availability of expertise in each modality’s application and interpretation. Currently, gravimetry is deemed as the experimental reference method and transpulmonary thermodilution as the clinical reference method, while lung ultrasonography stands for the promising tool.
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