Assessment of Pulmonary Edema: Principles and Practice

Abstract:

Pulmonary edema is increasingly recognized as a perioperative complication impacting outcome. Several risk factors have been identified including those of cardiogenic origin, such as heart failure or excessive fluid administration, as well as those related to increased pulmonary capillary permeability secondary to inflammatory mediators.

Effective treatment requires prompt diagnosis and early intervention. Consequently, the past two centuries have seen a concentrated effort to develop clinical tools to rapidly diagnose pulmonary edema and track response to treatment. The ideal properties of which include high sensitivity and specificity, easy availability, and the ability to diagnose early accumulation of lung water prior to the development of the full clinical presentation. In addition, clinicians highly value the ability to precisely quantify extravascular lung water accumulation and differentiate hydrostatic from high permeability etiologies of pulmonary edema.

In this review, we first discuss advances in understanding the physiology of extravascular lung water accumulation in health and in disease and the various mechanisms that protect against development of pulmonary edema under physiologic conditions. We then examine the various bedside modalities available to diagnose early accumulation of extravascular lung water and pulmonary edema including chest auscultation, chest roentgenography, lung ultrasonography and transpulmonary thermodilution. We explore the advantages and limitations of these methods for the

operating room and intensive care which are critical for proper modality selection in each individual case.

Introduction:

The lungs represent a unique organ in which air and blood are circulating efficiently, each in its own conduit without mixing with one another. Air circulates in its bronchial and alveolar conduits surrounded by blood circulating in a permeable and pressurized capillary network. Normally there is a balance between the net fluid filtered from the pulmonary circulation and the fluid absorbed by the lymphatic system. This balance ensures only a small volume of fluid is present in the interstitial space. Excessive accumulation of extravascular lung water (EVLW) is clinically manifested as pulmonary edema. This can result from an increase in the amount of filtered fluid secondary to marked increases in pulmonary hydrostatic pressure or an increase in the pulmonary capillary permeability, which causes water and proteins extravasation [1] or from interruption of the lymphatic drainage as in lung resection surgery [2]. Regardless of the etiology, the resultant fluid accumulation in the lung impairs respiratory gas exchange resulting in respiratory distress and the need for mechanical ventilation.

Pulmonary edema is increasingly recognized as a perioperative complication impacting outcome. Several factors have been identified e.g. fluid overload, systemic inflammatory response to surgery, myocardial ischemia, blood product transfusion, etc., all of which contribute to increased fluid transudation and accumulation of extravascular lung water [3] . Management strategies directed at avoiding excessive fluid administration (e.g. goal directed fluid therapy) or reducing inflammatory response (e.g. protective lung

ventilation to avoid ventilator induced lung injury) are commonly advocated in perioperative care protocols [1, 4-6 7].

Furthermore, pulmonary edema represents a significant burden to the healthcare system. A review of 8195 patients who underwent major inpatient operations in two university teaching hospitals revealed an incidence of pulmonary edema of 7.6% with an associated in hospital mortality rate of 11.9% [8]. Pulmonary edema is associated with higher morbidity rates and prolonged intensive care (ICU) stay, in which 15% will require mechanical ventilation [9]. Further, the addition of mechanical ventilation will extend the length of stay in the ICU [10]. As such this complication often results in a lose-lose proposition as it worsens patient outcomes while greatly increasing healthcare costs [11].

For decades, chest auscultation and roentgenography played a major role to diagnose pulmonary edema and monitor response to therapy. Our understanding of the inherent limitations of these two methods has led to the development of newer technologies that offer more sensitive detection of lung water changes in real time to better aid diagnosis and guide clinical interventions [12]. Of these, both the lung ultrasound (LUS) and transpulmonary thermodilution (TPTD) methods have now entered the clinical arena. The aim of this review is to provide an up to date examination of the recent advances in understanding the physiology of lung water dynamics in health and disease and to highlight the various bedside methods available to measure EVLW and diagnose pulmonary edema. There is special emphasis on the emerging role of LUS and TPTD as new tools to quantitatively measure EVLW in the perioperative period and provide early diagnosis of pulmonary edema.

Current Concepts in Pulmonary Fluid Dynamics

Extravascular Lung Water in Health and Disease:

It is a remarkable feat of engineering that prevents the air-filled alveoli and surrounding interstitium from being soaked by the neighboring pulmonary vessels. Pressurized and highly permeable, there is a strong motive force driving pulmonary capillary fluids across the microvascular endothelium into the interstitium and air sacs. Yet the interstitium is a relatively dry space with EVLW value of < 10 ml per kg of ideal body weight [13] .

The mechanism controlling fluid exchange between the microvascular and interstitial spaces proposed by Ernest Starling in 1896 shaped medical thinking for over a century. He concluded that the interplay of outward filtration forces created by the capillary hydrostatic pressure and the inward reabsorption forces from plasma protein oncotic pressure determined fluid exchange with the capillary endothelium acting as a semipermeable membrane [14].

Although this model became widely adopted as doctrine, a series of experimental data beginning in the 1940's raised doubts on its merit. The discovery that an endothelial surface layer lining the luminal side of the capillary endothelium, as first predicted by Danielli 1940 [15], and the non-linear relationship between hydrostatic pressure and vascular permeability, which represents a deviation from the classic Starling relationship, revolutionized the understanding of fluid dynamics [16-18].

Electron microscopy shows that the endothelial surface layer is lined with a complex network of glycosaminoglycans and proteins, which creates a gel like coating. The structure of this endothelial surface layer is called the endothelial glycocalyx (figure

1) [19]. This glycocalyx layer (EG) has recently been discovered to play a critical role in capillary fluid dynamics preventing excessive fluid extravasation. First, it acts as a molecular sieve limiting water and solute efflux across the intercellular junction. Second, it provides scaffolding upon which serum plasma proteins accumulate and consequently a layer of ultrafiltrate is created between the endothelium and the EG. This layer of ultrafiltrate creates a powerful oncotic force pulling fluid to the intravascular compartment. Breakdown of this layer, such as following surgical trauma and ischemic/reperfusion injuries, results in markedly increased capillary permeability (Figure 2) [17]. Lastly, the EG acts as a mechanosensor transmitting the shear stress from blood flow to the endothelium cytoskeleton initiating intracellular signaling which increases capillary permeability [16, 20]. Following a marked increase in capillary hydrostatic pressure, fluid extravasates out of the capillaries and accumulates in the interstitial space.

The emerging role of the EG has reshaped our current understanding of the pathophysiology of pulmonary edema. Either damage to this EG layer or marked increases in capillary hydrostatic pressure will lead to excessive fluid transudation into the interstitial space.

Role of pulmonary capillary pressure and hydrostatic edema:

The pulmonary capillary wedge pressure or left atrial pressure are clinically used as indicators of the pressure in the pulmonary microvasculature although they are not the same as the pulmonary capillary hydrostatic pressure. The relationship between pulmonary microvascular hydrostatic pressure and left atrial pressure can be estimated

by the following equation: $P_{mv} = P_{La} + 0.4 (MPAP - P_{La})$

Where P_{mv} is the Pulmonary microvascular hydrostatic pressure, P_{La} is left atrial pressure and MPAP is mean pulmonary pressure [21].

To mitigate EVLW accumulation following increases in capillary hydrostatic pressure and cardiac output, the pulmonary circulation exhibits several protective mechanisms namely, recruitment and distention of the pulmonary capillaries[22]. In an animal model, it was found that the extravascular lung water accumulation did not change significantly until microvascular hydrostatic pressure more than doubled; supporting a wide safety margin against rises in microvascular hydrostatic pressure [21, 23]. However, conditions associated with further rise in hydrostatic pressure, such as excessive fluid administration or heart failure can overwhelm these mechanisms resulting in fluid extravasation and pulmonary edema.

Role of lymphatics in fluid clearance:

The pulmonary lymphatics are present along the peribronchovascular, interlobular septae and the pleural spaces. These loose connective tissue spaces serve as a sump suction system draining fluid away from the alveolar interstitium in early stages of EVLW accumulation [24]. The effectiveness of this lymphatic sump drainage was demonstrated by Zarines et al., who showed that the lymph flow is about 20 ml/hr under normal conditions and increases 5-10 fold with chronic elevations in interstitial pressure [25]. Gee and Williams determined that water content contained by the peribronchiovascular cuffs increased 70% when transpulmonary pressure was increased to 20 cmH_20 [26]. Further accumulation of interstitial fluid is limited by the low

compliance of the interstitial compartment. This protective mechanism is short-lived secondary to fragmentation of interstitial proteoglycans causing loss of matrix integrity[27].

Progression to Pulmonary Edema:

Whether a result of increases in hydrostatic forces or increases in permeability, fluid accumulation progresses in a defined sequence. In stage 1 ("compensated"), fluid accumulation increases but is balanced by the increase in lymphatic flow causing no net accumulation of fluids. Stage 2 ("perihilar edema") develops when the lymphatic flow is overwhelmed by the increase in fluid accumulation and edema starts to develop surrounding the bronchioles and lung vasculature yielding the classic roentgenographic pattern of interstitial pulmonary edema (Kerley B lines, indistinct vessels, peribronchial cuffing, and). Stage 3 ("alveolar edema") develops following further accumulation of interstitial fluid which tracks first around the periphery of the alveolar membrane (stage 3a) and finally disrupting the alveolar wall causing alveolar flooding (stage 3b) which results in impairment in the gas exchange yielding the roentgenographic picture of alveolar pulmonary edema [28]. The ability to track the progression of lung water accumulation as well as to determine its causative etiology remains the Holy Grail for clinical assessment of pulmonary edema.

Clinical Techniques to assess extravascular lung water:

Auscultation:

Although symptoms and signs of the patient examination (tachypnea, orthopnea) can suggest pulmonary edema, it wasn't until the advent of chest auscultation, and later the development of the stethoscope, that clinicians had a more objective means to

assess lung edema. Auscultation remains a highly valued diagnostic tool in wide use today despite the development of more sophisticated technologies. The ability to diagnose different lung diseases by chest auscultation was initially explored by Hippocrates who placed his ears directly on the patient's chest to hear transmitted sounds and called this procedure "direct auscultation". The development of the stethoscope, first using a rolled paper cone and later a hollow wooden tube, by the French physician Dr. René Laënnec in the 19th century brought auscultation into the focus of clinical practice (Figure 3) [29]. Laennec, through extensive medical practice was the first to classify different breath sounds, which he then determined to be pathognomonic of pulmonary pathologies including pneumonia, bronchiectasis and pulmonary edema. In his landmark publication, *"A Treatise on the Diseases of the Chest and on Mediate Auscultation"*, he described the classic auscultatory findings in pulmonary edema as deep crepitus inspiratory râles which convey the impression of air entering and distending dry lungs [30].

Râles, a term that has been replaced by "crackles" in modern practice, remain the key diagnostic feature of auscultation in pulmonary edema. These are discontinuous, explosive and nonmusical adventitious sounds normally heard in inspiration. They are classified according to their duration, loudness and timing in the respiratory cycle as fine or coarse crackles (Figure 4) [31]. Importantly fine crackles are produced within small airways often impacted by interstitial edema whereas coarse crackles arise from large bronchi in processes such as pneumonia [32]. The mechanism of production of fine crackles is the snap opening of small airways during inspiration after being collapsed during expiration. In cardiogenic pulmonary edemas, crackles

occur due to opening of the small airways narrowed by peribronchial edema [33]. They are detected as high pitched, long duration sounds beginning in late inspiration. They are typically best appreciated in posterior basal regions in supine patients.

The stethoscope is an inexpensive, accessible bedside tool that has been in common practice for over a century, despite significant limitations of its usefulness. These limitations include wide inter-observer variability, inadequate understanding of the mechanism of sound production in different pathologies, failure to detect lung water accumulation in its early phases, and difficulty in monitoring the progression of the disease [34]. In a study on acute respiratory distress syndrome (ARDS) patients, lung auscultation had a diagnostic accuracy of 55% compared to thoracic computed tomography [35]. It was also shown to have a very low power to discriminate mild and moderate pulmonary congestion when compared to lung ultrasound in patients with end stage renal disease on hemodialysis[36].

Clinician's hearing loss due to increasing age or disease is an additional limitation of stethoscopy [37]. Stethoscopes compatible with hearing aids and electronic stethoscopes using sophisticated mathematical models have been introduced into clinical practice in an attempt to overcome some of the limitations and improve its sensitivity and specificity for lung water detection [38, 39].

The stethoscope remains an important part of the physical examination, but because of its shortfalls, it is becoming a decorative instrument for many practitioners who increasingly rely on more sensitive and reliable technologies.

Chest Roentgenography:

The chest roentgenogram has been relied on to diagnose and follow the progression of pulmonary edema for decades. It quickly established itself as the standard reference technique against which other methods to measure lung water content were compared. It offers the advantages of being widely available, reproducible, noninvasive, portable and relatively low in cost.

Standard imaging utilizes the postero-anterior and lateral views, or in the case of portable exams, the anteroposterior view. *Interstitial* features of pulmonary edema manifest radiographically as peribronchial cuffing, indistinct vessels, and septal (Kerley) lines (Figure 5). In distinction, *alveolar* features present with acinar opacities, ground glass opacities, and frank consolidations (Figure 6). The appearance of these features along with patterns of distribution and other accompanying findings can be used as clues to the cause and severity of the pulmonary edema. Table 1 highlights the radiographic findings associated with disease severity. For example, stage 2 pulmonary edema appears as a perihilar process while the more severe stage 3 appears as a generalized flooding of the lung fields [40-43].

Radiologists often seek out a pattern of chest roentgenogram findings to differentiate between cardiogenic (e.g., congestive heart failure, CHF), noncardiogenic (e.g., ARDS), and fluid overload (e.g., renal failure) causes of edema (Table 2) [44, 45]. Using these chest roentgenogram features, Milne et al showed an average of 91% accuracy in distinguishing capillary permeability edema from other varieties, and 81% accuracy in distinguishing cardiogenic edema from that of renal failure [44].

Gluecker et al offered further insight into radiographic patterns to allow differentiation between a myriad of causes of pulmonary edema. For example, the bilateral perihilar alveolar edema appearance “bat-wing” in patients with acute severe CHF or renal failure that can improve rapidly with aggressive treatment. Septal lines, peribronchial cuffing and, if severe, alveolar edema are markers for negative pressure or post obstructive edema. Kerley lines, peribronchial cuffing and patchy perihliar airspace consolidation are seen in near-drowning cases. Bilateral homogeneous airspace consolidation favoring upper lobes is typical of neurogenic edema. Central interstitial edema (peribronchial cuffing, indistinct vessels) and asymmetrical patchy airspace consolidation are findings in high-altitude edema. A spectrum from modest interstitial (Kerley lines, peribronchial cuffing and indistinct vessels) to severe alveolar (consolidation) is seen in postpneumonectomy edema [42]. Accordingly, the ability of chest roentgenogram patterns to differentiate pathology and predict response to therapy is highly valued in the clinical setting.

From a physiological standpoint, radiographic features of acute cardiogenic pulmonary edema generally correlate with the pulmonary capillary wedge pressures. The chest roentgenogram can be normal with mildly elevated pressures, but with increasing pressures and fluid transudation, various features become evident [42,43]. Early on, in cardiac compromise and/or volume overload, radiographic findings of enlarged heart, engorged upper lobe vessels, or widened vascular pedicle are considered “pre-edema” features. With progressive EVLW accumulation, the chest roentgenogram typically begins to show features associated with pulmonary edema (e.g., Kerley lines, indistinct vessels, peribronchial cuffing, and airspace opacities).

Despite these advantages, the clinical environment has shown substantial limitations with chest roentgenographic monitoring. For example, the well described relationship between pathology and imaging has a clinical correlation that is less than desired [46, 47]. In addition, there is often a time lag of up to 12 hours after the clinical and physiological manifestations of CHF to the appearance of radiographic findings due to the relatively slow movement of water through the widened capillary endothelial cell junction. Similarly, with resolution of pulmonary edema, the radiographic findings will persist for 1 to 4 days after the physiologic and clinical improvement [46]. Limitations in accuracy also must be considered. In the diagnosis of alveolar-interstitial pulmonary edema the accuracy of chest roentgenogram was shown to be only 72% compared to computed tomography in a case-control study [35]. In a study of ARDS patients, chest roentgenogram was modestly correlated with transpulmonary thermodilution measured EVLW. The authors noted chest roentgenogram lacked quantitative measurement of EVLW that can be advantageous to guide fluid management and was insensitive to detection of small changes in EVLW and failed to predict mortality compared to transpulmonary thermodilution [48]. In an animal study, chest radiography did not detect EVLW until lung water had increased by > 35% [49]. Although, chest roentgenogram was able to distinguish temporal changes in lung water in critically ill patients randomized to receive a diuretic or placebo [50], it failed to accurately monitor modest changes in lung water [51].

The degree of interobserver variation in chest roentgenography represents another concern. In a study of 21 expert radiologists selected to review 28 chest radiographs of ARDS patients under mechanical ventilation, the interobserver variability

ranged from 36 to 71% in diagnosing ARDS according to the American-European consensus Conference definition of ARDS [52]. Many anesthesiologists practicing in intensive care units make important clinical decisions guided by radiographic interpretations. Given the challenges faced by radiologists, it is no surprise the radiographic interpretation in patients with significant pulmonary diseases can exceed the skills of many anesthesiologists [53].

The suboptimal quality of portable images is another disadvantage, which particularly impacts perioperative and critical care clinicians. In portable, supine radiographs, the evaluation of heart and vessel size is limited, however, alveolar and interstitial edema, and possibly pleural effusions, can still be evaluated. Similarly, chest fluoroscopy is not preferred to evaluate for pulmonary edema because its fidelity for assessment of fluid accumulation is even inferior to that of a portable chest radiograph (e.g., evaluation of pulmonary vessels, bronchial walls, interstitial lines, etc.) [54]. In current practice the use of fluoroscopy is out of favor as the digital chest radiograph can be obtained portably and is almost instantly available for review.

Regardless of technique, chest roentgenography lacks the fidelity obtained with computed tomography (CT) where the extent and characterization of airspace disease (ground glass opacity and consolidation) is more vividly portrayed, as are certain interstitial features such as septal lines and pleural effusions. And although the radiation exposure of a chest roentgenogram is far less than that of CT, cumulative radiation exposure with repeated examinations remains a concern.

Despite these shortfalls, chest roentgenography continues to be widely used as a tool to monitor pulmonary edema in intensive care units. However, clinical desire for

more accurate and timely guidance of fluid therapy and more sensitive detection of early lung water changes are leading to the adoption of newer technologies.

Lung Ultrasonography:

Lung Ultrasound (LUS) has become a valuable point of care (POC) tool in the assessment of acute pulmonary pathologies in the intensive care unit, emergency department, and operating room. Based on visualization of anatomical structures, pathological findings, and acoustic artifacts, specific image patterns can be identified for the differentiation of a variety of pulmonary- and pleural disease-states [55]. While healthy lung tissue is poorly penetrated by ultrasound due to the high acoustic impedance of air, the presence of EVLW results in occurrence of so-called B-lines or lung comets which are formed as a result of acoustic reverberation artifacts arising from the air-fluid interface between collapsed, fluid-filled, and aerated alveoli [56, 57].

First described in 1982 [58], specific characteristics distinguish B-lines from other artifacts seen on LUS, and they represent the core-imaging finding used in the evaluation of pulmonary edema. Sonographic appearance of normal lung tissue is defined by “black” lung with sliding movement of visceral and parietal pleura against each other, and horizontal reverberation artifact of the pleural line in equal distance termed A-lines as shown in video 1.

B-lines are well-defined, hyperechoic artifacts, arising from the pleural line fanning down into the far field of the screen without fading (Figure 7). While healthy lung tissue may display 3-4 B-lines correlating with radiographic Kerley B-lines, the presence of more than three B-lines (also called lung rockets) is indicative of interstitial edema.

With further increase in EVLW, a rising number of B-lines are seen in narrower distance apart, and they can merge to display ground glass rockets, also called “white lung”, seen in severe states of alveolar-interstitial syndrome (AIS) (Figure 8) [59]. Sonographic appearance of AIS can be seen with multiple underlying pathologies such as cardiogenic pulmonary edema (APE), acute respiratory distress syndrome (ARDS), or pulmonary fibrosis, and only identification of AIS on LUS in conjunction with other pathologic image-patterns enables the skilled sonographer to differentiate these etiologies (Table 3) [60]. AIS in the setting of left atrial hypertension and increased hydrostatic pressure often shows a uniform distribution pattern of B-lines, with normal lung sliding and a high incidence of homogeneous appearing pleural effusions. In contrast, ultrasound findings suggestive of ARDS include increased amounts of B-lines seen in combination with pleural line abnormalities, lack of lung sliding, uneven tissue patterns like “spared areas” and consolidations and consolidation-associated findings such as “lung pulse” (which is defined as the absence of lung sliding with the perception of heart activity at the pleural line) and air-bronchograms (Figure 9).

When pattern-recognition is used in an algorithmic approach like the Bedside Lung Ultrasound in Emergency (BLUE) protocol, LUS has a diagnostic accuracy of > 95% sensitivity and specificity for a broad variety of pulmonary and pleural pathologies [61, 62]. This contrasts with chest roentgenogram or clinical examination including auscultation or both that showed a sensitivity of 7- 14 % in patients with documented AIS by LUS in the perioperative period of cardiac surgery [63].

The correlation of B-line artifacts as a marker of increased EVLW show similar high accuracy with sensitivities and specificities of > 90% when compared to multiple classic

methods of assessing EVLW like computed tomography of the chest [62, 64], chest roentgenogram [35, 65], pulmonary occlusion pressures [66, 67], brain natriuretic peptide (BNP) measurements [68], or transpulmonary thermodilution (TPTD) method to measure EVLW [66]. In addition, the linear correlation between quantity of B-lines, amount of EVLW, and clinical pulmonary edema has been well recognized, and application of quantitative algorithms, like lung comet scores, may provide a useful clinical tool in the daily POC assessment for pulmonary edema [65, 66, 69].

Over the last decade multiple studies have established good temporal correlation between amount of EVLW and the onset and resolution of B-lines [65, 66, 70]. In addition, Caltabeloti et al found that loss in lung aeration in septic patients receiving fluid-resuscitation, could be detected by LUS within a 40-minute timeframe, even before changes in oxygenation by partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio [71]. Furthermore, the immediate dynamic changes of B-lines in correlation to volume removal in patients while undergoing hemodialysis was shown in renal failure patients undergoing hemodialysis [72, 73]. These findings confirm the clinical advantage of LUS in the immediate and dynamic feedback of severity of pulmonary edema when compared to chest radiograph.

The clinical use of LUS in evaluating increases in EVLW is ample. It ranges from initial POC diagnostic for respiratory failure to guidance of patient care, to finally, follow-up monitoring of performed clinical interventions. Currently the overwhelming use remains in the diagnosis and management of respiratory failure and guidance in volume resuscitation. Standardized algorithms used for the assessment of EVLW and lung pathologies optimize sensitivity and specificity while making it a fast and practical tool in

the daily clinical management [69, 74, 75]. In a study of patients undergoing cardiac surgery, the combined use of transthoracic echocardiography and lung ultrasound was shown to change the clinical management in 67% of the patients. Furthermore, lung ultrasound was able to detect alveolar-interstitial disease that was missed by clinical examination and chest roentgenography [76].

Utilizing 5-13 MHz linear array, or 1 – 6 MHz phased array ultrasound probes, multimodal scanning of the anterior and lateral lung at different locations is applied to achieve a panoramic impression of the complete lung and pleura [77]. While most of the literature focuses on the advantages, accuracy, and feasibility of LUS for the diagnosis of pulmonary edema and other pathologies, little data has been published on outcomes when used to guide patient management. One study by Frassi et al, showed that LUS is a more powerful predictor for significant events in patients with symptoms of dyspnea or chest pain on hospital admission than echocardiographic variables [78]. Additionally, Soummers et al suggested a predictive value of LUS in the weaning process from mechanical ventilation. In their study, B-lines predominance were associated with increased respiratory failure post extubation [79].

The advantages of LUS as an economic, fast, and real-time imaging modality for diagnosis and surveillance of clinical relevant pathologies has positioned the technique at the center of POC diagnostics in critical care medicine, emergency medicine, and anesthesiology. It's high accuracy and absence of radiation exposure surpasses its confinements as a non-panoramic imaging modality compared to chest roentgenogram or computed tomography in the daily management of patients.

Variability of practitioner knowledge and lack in standardized training are challenges to the expanded use of LUS. To address these concerns, the American College of Chest Physicians (ACCP) and La Société de Réanimation de Langue Francaise published a joint statement on competence in critical are ultrasonography [80]. In anesthesiology and other medical disciplines, training programs being initiated to ensure uniformity and consistency in education and the evaluation of proficiency for the use of ultrasound [81,82].

Transpulmonary Thermodilution:

Transpulmonary thermodilution 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 arteries) resulting in recording of a thermodilution curve. A variety of physiologic parameters including cardiac output, intrathoracic volumes, and extravascular lung water are obtained from this curve. The presence of pulmonary edema results in a heat sink with increased indicator loss (i.e. warming of the fluid bolus) during pulmonary transit. This loss of indicator is used to quantify extravascular lung water. The calculation of EVLW using the TPTD method is beyond the scope of this review. A detailed review of this technique is available in our previous publication [3]. As such, clinical measurement of EVLW reflects a morphologic correlate of pulmonary edema [83].

Compelling evidence supports the ability of TPTD to characterize progressive accumulation of pulmonary edema. In a porcine model of hydrostatic pulmonary edema, Bongard et al demonstrated the association between EVLW and the classical histological progression of pulmonary edema [83]. EVLW measurements has strong linear

association with increases in perivascular cuff width to vessel diameter ratio (r=0.87; p<0.0001), inter-alveolar septal width (r=0.89; p<0.001) and (once present) alveolar flooding (r=0.87; p<0.001) [83].

The sensitivity of TPTD to detect early and small changes in pulmonary edema is another strong asset to this modality. Fernandez-Mondejar et al examined the ability of TPTD EVLW measurement to detect 'small changes' in EVLW in pigs both with and without pulmonary edema [84]. By measuring EVLW immediately before and after intratracheal administration of 50 ml of saline solution [so increasing EVLW (alveolar fluid) by 50ml], they demonstrated that TPTD could detect these modest increases in EVLW. Putting these results in context with the observations of Bongard et al [83] which suggest that increases in EVLW in excess of 100% are required before the onset of hypoxemia or histological changes, makes the exciting suggestion that EVLW measurement may be able to sensitively detect sub-clinical increases in EVLW, potentially facilitating early intervention.

Several authors have demonstrated modest association between chest roentgenogram scores and TPTD derived EVLW [85-87]. The existence of only modest association between two modalities, ostensibly measuring the same thing, may reflect the superior sensitivity and specificity of EVLW measurement; increased chest roentgenogram opacity is not *specific* to the existence of pulmonary edema, whilst the superior sensitivity of TPTD for small increases in EVLW means that EVLW may exist, be measureable by TPTD but undetectable by chest roentgenogram.

Another major advantage of the TPTD technique to measure pulmonary edema over imaging modalities is its inherent reproducibility. Both TPTD monitors available for

clinical use (Figure 10) [88, 89] achieve values for the co-efficient of variation (CV) of EVLW ranging from 4.8 to 8% [90, 91]; well within the 15% threshold of CV which has been suggested as a cut-off for clinical acceptability [92]. In practice, manual inspection of thermodilution curves at the time of measurement allows clearly spurious measurements to be discarded and adds further increased reliability.

TPTD requires central venous and arterial cannulation, limiting hospital wide application of the technique. In patients in intensive care or during the perioperative period where invasive monitoring is commonplace however, TPTD derived EVLW measurement has many benefits. Once TPTD monitoring is established, junior medical or non-medical staff with the minimum of training may easily and rapidly perform a series of thermodilution measurements. This ease of use and the absence of ionizing radiation means EVLW can be repeatedly determined multiple times a day, allowing trends to be observed and an evaluation of response to therapy is monitored.

In addition to providing an index of the presence and severity of pulmonary edema, TPTD also offers the potential to aid the clinician in determining the etiology of edema. Measurement of EVLW in the context of cardiac preload [93] (i.e. calculation of the ratio of EVLW to cardiopulmonary blood volume can provide a means to estimate pulmonary vascular permeability. Intrathoracic blood volume (ITBV) [93-95], global end-diastolic volume (GEDV) [94, 96] and pulmonary blood volume (PBV) [94-96] are indices of cardiac preload derived from TPTD to which EVLW has been indexed in the derivation of 'pulmonary vascular permeability indices' (PVPIs). The concept is intuitive; a high EVLW in a hypovolemic patient (and therefore an elevated ratio) suggests increased

capillary permeability as the primary pathology whilst high EVLW in a patient with elevated preload (normal ratio) suggests increased hydrostatic forces.

TPTD methods for measuring EVLW can only measure lung water in perfused areas of lung and so rely upon a homogeneous distribution of pulmonary perfusion to accurately determine EVLW. A large perfusion deficit will lead to underestimation of EVLW. Regional pulmonary perfusion is influenced by many factors pertinent to the perioperative critically ill population. Hypoxic pulmonary vasoconstriction [97], lung injury [98], vascular obstruction [99], positive end-expiratory pressure [100, 101], spontaneous breathing [102] and lung resection [103] can all influence ventilation-perfusion relationships and so lead to errors in the estimation of EVLW.

It is plausible that the presence of pleural or pericardial effusions could provide a further extravascular fluid volume into which cold indicator could distribute, leading to an artefactual over-estimate of the EVLW volume. Blomqvist et al systematically evaluated the effects of incremental increases in pleural fluid volume (warmed normal saline introduced bilaterally via intercostal catheters) on EVLW in otherwise healthy dog lungs. They reported a slight, but not statistically significant rise in EVLW and though *"a minor, and for practical purposes negligible loss of thermal indicator to the pleural fluid could not be excluded",* they ultimately concluded that installation of up to 20 ml/kg of fluid into the pleural cavity has no effect on EVLW [104]. Similarly, several clinical studies in medical intensive care patients undergoing thoracentesis have demonstrated no effect of pleural effusion on EVLW measurement [105, 106].

In summary, EVLW together with other TPTD derived parameters offers an insight to clinicians to explore and portray patient's hemodynamic instability in depth.

TPTD derived EVLW offers a unique means to quantify and early diagnose pulmonary edema, track the progression and response to therapy and help differentiate its etiology. Its relative invasive nature limits its use to hemodynamically unstable patients in the intensive care units or to the operating room to patients undergoing surgeries that carry a high risk for lung injury e.g. major cardiothoracic and vascular surgery.

Modality Selection:

In current practice the practitioner's selection amongst auscultation, chest roentgenogram, lung ultrasound, and transpulmonary thermodilution to assess pulmonary edema is influenced by clinical and institutional factors. The demands of the case at hand, along with the expertise and resources available in the clinical setting dictate the modality employed. To aid in this selection process, the advantages and limitations of the various modalities in the clinician's armamentarium are summarized in Table 4.

Stethoscopy remains an important component of the initial clinical examination. As a tool, it shows high specificity but at the cost of low sensitivity, lacking in early detection of pulmonary congestion with a limited ability to inform on the severity of pulmonary edema. As such it is recommended primarily as a readily available and inexpensive screening tool.

Chest roentgenography remains the modality of choice in post anesthesia care units and intensive care units to initially diagnose, profile the etiology, and subsequently monitor patients with pulmonary edema. Its panoramic view of the chest helps clinicians identify additional pulmonary pathologies co-existing with pulmonary edema.

To avoid clinical errors, clinicians must remain cognizant of the limited accuracy of chest roentgenogram for both early detection and grading of the severity of EVLW accumulation. As such, chest roentgenogram is another modality with high specificity and low sensitivity. Further, the temporal changes in the radiographic evidence of pulmonary congestion lag the clinical manifestations both in its detection of the onset of pulmonary edema and its resolution. Despite these limitations, resource availability and the wealth of information provided by chest roentgenograms and the availability of expert radiologists for interpretation continue to support its widespread use in current practice.

Lung ultrasonography is a recent advance that addresses many of the limitations inherited by chest auscultation and chest roentgenogram. It has the advantage of detection of early phases of EVLW accumulation prior to clinical manifestations allowing the clinician to implement clinical interventions prior to overt clinical manifestations. Its property of higher specificity and sensitivity than seen with prior techniques promotes its use both as an initial screening modality and as a monitor. One of its most useful applications is in the perioperative period for early detection of acute interstitial pulmonary edema especially in patients present for surgery without any preoperative respiratory symptoms. Its noninvasiveness, including no ionizing radiation, has led to lung ultrasound frequently being used in conjunction with or as a replacement for chest roentgenograms. However, in contrast to chest radiography that is supported by specialized radiology technicians and physicians, the lack of available personnel with skill in performance and interpretation of lung ultrasound limits its use in many institutions. This remains an educational challenge for our training institutions.

Invasive hemodynamic monitors are frequently required during major surgical procedures, such as cardiac, major vascular or thoracic surgery, or in clinical conditions such as septic shock that carry a high risk for lung injury. In these patients, transpulmonary thermodilution offers unique advantages. It provides several hemodynamic indices to guide therapeutic management. In addition, the ability to quantitatively measure EVLW accumulation at its earliest phase and assess its progression or improvement is particularly advantageous to these patients' groups. As such, TPTD monitoring offers a combination of benefits not obtainable by other modalities. Recognizing that its invasiveness limits its use to select patients, the information provided by TPTD is currently unrivaled by competing technologies.

Conclusion:

Pulmonary edema is a long recognized morbid condition. In response, the past two centuries have witnessed the development of a series of technological approaches for its detection and monitoring. Today's clinician benefits from an armamentarium of devices to assess lung water, each of which best suited to a particular application. The selection of modality for the case at hand requires not only an understanding of the unique advantages and limitations of these approaches but also on the availability of expertise in their application and interpretation.

Figures and video Legends:

Figure 1:

Electron microscopy reveals vascular capillary in cross section and its associated endothelial glycocalyx layer. (Adapted from Rehm et al.[19]).

Figure 2:

A- An intact endothelial glycocalyx covers the luminal endothelial surface and cell-cell junctions limiting water and electrolyte efflux.

B- Breakdown of the glycocalyx layer, such as seen following surgery or ischemic/reperfusion injury, results in increased vascular permeability and pulmonary edema.

(Adapted from Collins et al. [17]).

Figure 3

Laënnec's stethoscope.

A) Photo courtesy of the US National Library of Medicine.

1) Instrument assembled

2) and 3) two portions of the instrument in longitudinal section

4) Detachable chest piece

5) Ear piece unscrewed;

6) Transverse section.

B. Laënnec and the Stethoscope. Painting by Robert A.Thom (1915-1979), c.1960.

(Adapted from Roguin A. **[29])**.

Figure 4:

Classification of pulmonary crackles.

ll Time in milliseconds from the onset of the crackle until the first deflection returns to the baseline. (Adapted from Andrews J and Badger T. [31]).

Figure 5:

Chest roentgenogram features of cardiogenic pulmonary edema.

Figure 6:

Chest roentgenogram features of acute respiratory distress syndrome showing patchy opacities, the indistinct vessels signify interstitial edema, while the airspace disease signifies alveolar edema.

Figure 7:

Normal lung ultrasound.

A) A-lines reverberation artifact in equal distance (arrows).

B) B-lines (stars) arising as well-defined echogenic comet tail from the pleural line throughout the entire US image. LUS = lung ultrasound.

Figure 8:

CXR and LUS of normal lung and AIS.

A) Normal AP-CXR. B) CXR in mild AIS. C) CXR in severe AIS. D) US findings of normal lung tissue with A-lines (arrows) and B-line (star), smooth pleural interface and homogenous lung tissue. E) US findings of mild interstitial pulmonary edema with lung rockets (stars). F) US findings in severe AIS with ground glass rockets or “white Lung”, with persistent smooth pleural line and homogeneous lung tissue suggestive of severe pulmonary edema secondary to APE.

CXR= chest radiography, AP = anteroposterior, LUS = lung ultrasound,

AIS = alveolar-interstitial syndrome, APE = acute cardiopulmonary edema.

Figure 9:

Lung ultrasound of alveolar interstitial syndrome. Acute cardiogenic edema vs ARDS.

A) Lung ultrasound findings suggestive of alveolar interstitial syndrome secondary to acute cardiogenic edema include: ground glass rockets or “white Lung”, with persistent smooth pleural line and homogeneous lung tissue.

B) Lung ultrasound findings suggestive of alveolar interstitial syndrome secondary to severe ARDS include: “white lung” in combination with thickened and uneven pleural line, inhomogeneous lung tissue and air bronchograms (arrows)

ARDS = adult respiratory distress syndrome.

Figure 10:

Screenshots from 2 proprietary transpulmonary thermodilution systems commercially available. A) The PiCCO2 system (Pulsion Medical Systems SE, Munich, Germany) and B) The VolumeView/EV1000 system (Edwards Life sciences, Irvine CA).

CI = Cardiac index, ELWI = Extravascular lung water index, GEDI = global end diastolic index, PCCI = Pulse contour cardiac index, $ScVo_2$ = Mixed venous oxygen saturation, SVI = Stroke volume index, SVV = Stroke volume variation.

Video 1:

Two-dimensional ultrasound imaging of lung sliding in the normal lung. The pleural line can be seen as a fine horizontal echogenic line in the center of the image. Vertical artifacts with characteristics of B-lines arise from the pleural line. They are long non-fading, well-defined, hyperechoic comet-tail artifacts that move with lung sliding. An A-line being “erased” by the B-line can be seen at the bottom of the image.

References

1. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al.: Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 238:641-648, 2003.

2. Jordan S, Mitchell JA, Quinlan GJ, et al.: The pathogenesis of lung injury following pulmonary resection. Eur Respir J. 15:790-799, 2000.

3. Assaad S, Shelley B, Perrino A: Transpulmonary Thermodilution: Its Role in Assessment of Lung Water and Pulmonary Edema. J Cardiothorac Vasc Anesth. 2017.

4. Cannesson M: Arterial pressure variation and goal-directed fluid therapy. J Cardiothorac Vasc Anesth. 24:487-497, 2010.

5. Bellamy MC: Wet, dry or something else? Br J Anaesth. 97:755-757, 2006.

6. Licker M, Diaper J, Villiger Y, et al.: Impact of intraoperative lung-protective interventions in patients undergoing lung cancer surgery. Crit Care. 13:R41, 2009.

7. Severgnini P, Selmo G, Lanza C, et al.: Protective mechanical ventilation during general anesthesia for open abdominal surgery improves postoperative pulmonary function. Anesthesiology. 118:1307-1321, 2013.

8. Arieff AI: Fatal postoperative pulmonary edema: pathogenesis and literature review. Chest. 115:1371-1377, 1999.

9. Edoute Y, Roguin A, Behar D, et al.: Prospective evaluation of pulmonary edema. Crit Care Med. 28:330-335, 2000.

10. Hubble MW, Richards ME, Wilfong DA: Estimates of cost-effectiveness of prehospital continuous positive airway pressure in the management of acute pulmonary edema. Prehosp Emerg Care. 12:277-285, 2008.

11. Dasta JF, McLaughlin TP, Mody SH, et al.: Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med. 33:1266-1271, 2005.

12. Perel A, Saugel B, Teboul JL, et al.: The effects of advanced monitoring on hemodynamic management in critically ill patients: a pre and post questionnaire study. J Clin Monit Comput. 30:511-518, 2016.

13. Katzenelson R, Perel A, Berkenstadt H, et al.: Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water. Crit Care Med. 32:1550-1554, 2004.

14. Starling EH: On the Absorption of Fluids from the Connective Tissue Spaces. J Physiol. 19:312-326, 1896.

15. Danielli JF: Capillary permeability and oedema in the perfused frog. J Physiol. 98:109-129, 1940.

16. Dull RO, Mecham I, McJames S: Heparan sulfates mediate pressure-induced increase in lung endothelial hydraulic conductivity via nitric oxide/reactive oxygen species. Am J Physiol Lung Cell Mol Physiol. 292:L1452-1458, 2007.

17. Collins SR, Blank RS, Deatherage LS, et al.: Special article: the endothelial glycocalyx: emerging concepts in pulmonary edema and acute lung injury. Anesth Analg. 117:664-674, 2013.

18. Tarbell JM, Demaio L, Zaw MM: Effect of pressure on hydraulic conductivity of endothelial monolayers: role of endothelial cleft shear stress. J Appl Physiol (1985). 87:261-268, 1999.

19. Rehm M, Bruegger D, Christ F, et al.: Shedding of the endothelial glycocalyx in patients undergoing major vascular surgery with global and regional ischemia. Circulation. 116:1896-1906, 2007.

20. Weinbaum S, Tarbell JM, Damiano ER: The structure and function of the endothelial glycocalyx layer. Annu Rev Biomed Eng. 9:121-167, 2007.

21. Erdmann AJ, 3rd, Vaughan TR, Jr., Brigham KL, et al.: Effect of increased vascular pressure on lung fluid balance in unanesthetized sheep. Circulation research. 37:271-284, 1975.

22. West J: Respiratory Physiology: The Essentials. Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins, 2008.

23. Dull RO, Cluff M, Kingston J, et al.: Lung heparan sulfates modulate K(fc) during increased vascular pressure: evidence for glycocalyx-mediated mechanotransduction. Am J Physiol Lung Cell Mol Physiol. 302:L816-828, 2012.

24. Staub NC: Clinical use of lung water measurements. Report of a workshop. Chest. 90:588-594, 1986.

25. Zarins CK, Rice CL, Peters RM, et al.: Lymph and pulmonary response to isobaric reduction in plasma oncotic pressure in baboons. Circulation research. 43:925-930, 1978.

26. Gee MH, Williams DO: Effect of lung inflation on perivascular cuff fluid volume in isolated dog lung lobes. Microvascular research. 17:192-201, 1979.

27. Miserocchi G, Negrini D, Passi A, et al.: Development of lung edema: interstitial fluid dynamics and molecular structure. News in physiological sciences : an international journal of physiology produced jointly by the International Union of Physiological Sciences and the American Physiological Society. 16:66-71, 2001.

28. Naureckas ET, and Lawrence D. H. Wood. : "The Pathophysiology of the Circulation in Critical Illness.". in Hall JB (ed): Principles of Critical Care, 4e., New York, NY: McGraw-Hill, 2015, pp. http://accessmedicine.mhmedical.com/content.aspx?bookid=1340&Sectionid=80030661.

29. Roguin A: Rene Theophile Hyacinthe Laennec (1781-1826): the man behind the stethoscope. Clin Med Res. 4:230-235, 2006.

30. Laennec RTH, Forbes J: A treatise on the diseases of the chest and on mediate auscultation. (ed From the 4th London). Philadelphia, Desilver, Thomas, 1835.

31. Andrews JL, Jr., Badger TL: Lung sounds through the ages. From Hippocrates to Laennec to Osler. JAMA. 241:2625-2630, 1979.

32. Sarkar M, Madabhavi I, Niranjan N, et al.: Auscultation of the respiratory system. Ann Thorac Med. 10:158-168, 2015.

33. Forgacs P: Crackles and wheezes. Lancet. 2:203-205, 1967.

34. Loudon R, Murphy RL, Jr.: Lung sounds. Am Rev Respir Dis. 130:663-673, 1984.

35. Lichtenstein D, Goldstein I, Mourgeon E, et al.: Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. Anesthesiology. 100:9-15, 2004.

36. Torino C, Gargani L, Sicari R, et al.: The Agreement between Auscultation and Lung Ultrasound in Hemodialysis Patients: The LUST Study. Clin J Am Soc Nephrol. 11:2005-2011, 2016.

37. Rabinowitz P, Taiwo O, Sircar K, et al.: Physician hearing loss. Am J Otolaryngol. 27:18-23, 2006.

38. Yang F, Ser W, Yu J, et al.: Lung water detection using acoustic techniques. Conf Proc IEEE Eng Med Biol Soc. 2012:4258-4261, 2012.

39. Kah Jun H, Wee S, Foo DC: An analysis of sounds for lungs with excessive water. Conf Proc IEEE Eng Med Biol Soc. 2016:3662-3665, 2016.

40. Novelline R: Squires Fundamentals of Radiology, Harvard University Press, 2004.

41. Davies MK, Gibbs CR, Lip GY: ABC of heart failure. BMJ. 320:297-300, 2000.

42. Gluecker T, Capasso P, Schnyder P, et al.: Clinical and radiologic features of pulmonary edema. Radiographics. 19:1507-1531; discussion 1532-1503, 1999.

43. Milne E, Pistolesi M: Reading the chest radio-graph: a physiologic approach. St Louis, MO, Mosby-Year Book, 1993, pp. 9-50.

44. Milne EN, Pistolesi M, Miniati M, et al.: The radiologic distinction of cardiogenic and noncardiogenic edema. AJR Am J Roentgenol. 144:879-894, 1985.

45. Komiya K, Ishii H, Murakami J, et al.: Comparison of chest computed tomography features in the acute phase of cardiogenic pulmonary edema and acute respiratory distress syndrome on arrival at the emergency department. J Thorac Imaging. 28:322-328, 2013.

46. Kostuk W, Barr JW, Simon AL, et al.: Correlations between the chest film and hemodynamics in acute myocardial infarction. Circulation. 48:624-632, 1973.

47. Cardinale L, Volpicelli G, Lamorte A, et al.: Revisiting signs, strengths and weaknesses of Standard Chest Radiography in patients of Acute Dyspnea in the Emergency Department. J Thorac Dis. 4:398-407, 2012.

48. Brown LM, Calfee CS, Howard JP, et al.: Comparison of thermodilution measured extravascular lung water with chest radiographic assessment of pulmonary oedema in patients with acute lung injury. Ann Intensive Care. 3:25, 2013.

49. Snashall PD, Keyes SJ, Morgan BM, et al.: The radiographic detection of acute pulmonary oedema. A comparison of radiographic appearances, densitometry and lung water in dogs. Br J Radiol. 54:277-288, 1981.

50. Martin GS, Ely EW, Carroll FE, et al.: Findings on the portable chest radiograph correlate with fluid balance in critically ill patients. Chest. 122:2087-2095, 2002.

51. Halperin BD, Feeley TW, Mihm FG, et al.: Evaluation of the portable chest roentgenogram for quantitating extravascular lung water in critically ill adults. Chest. 88:649-652, 1985.

52. Rubenfeld GD, Caldwell E, Granton J, et al.: Interobserver variability in applying a radiographic definition for ARDS. Chest. 116:1347-1353, 1999.

53. Kaufman B, Dhar P, O'Neill DK, et al.: Chest radiograph interpretation skills of anesthesiologists. J Cardiothorac Vasc Anesth. 15:680-683, 2001.

54. Westra D, Sperber M: Conventional Chest Radiography, in Sperber M (ed): Radiologic Diagnosis of Chest Disease, 2nd edition, Springer-Verlag London Limited, 2001, pp. 40-41.

55. Lichtenstein DA: Lung ultrasound in the critically ill. Ann Intensive Care. 4:1, 2014.

56. Soldati G, Inchingolo R, Smargiassi A, et al.: Ex vivo lung sonography: morphologic-ultrasound relationship. Ultrasound Med Biol. 38:1169-1179, 2012.

57. Picano E, Pellikka PA: Ultrasound of extravascular lung water: a new standard for pulmonary congestion. Eur Heart J. 37:2097-2104, 2016.

58. Ziskin MC, Thickman DI, Goldenberg NJ, et al.: The comet tail artifact. J Ultrasound Med. 1:1-7, 1982.

59. Lichtenstein DA, Meziere GA, Lagoueyte JF, et al.: A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. Chest. 136:1014-1020, 2009.

60. Copetti R, Soldati G, Copetti P: Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. Cardiovasc Ultrasound. 6:16, 2008.

61. Lichtenstein DA, Meziere GA: Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. Chest. 134:117-125, 2008.

62. Volpicelli G, Mussa A, Garofalo G, et al.: Bedside lung ultrasound in the assessment of alveolar-interstitial syndrome. Am J Emerg Med. 24:689-696, 2006.

63. Ford JW, Heiberg J, Brennan AP, et al.: A Pilot Assessment of 3 Point-of-Care Strategies for Diagnosis of Perioperative Lung Pathology. Anesth Analg. 124:734-742, 2017.

64. Lichtenstein D, Meziere G, Biderman P, et al.: The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. Am J Respir Crit Care Med. 156:1640-1646, 1997.

65. Jambrik Z, Monti S, Coppola V, et al.: Usefulness of ultrasound lung comets as a nonradiologic sign of extravascular lung water. Am J Cardiol. 93:1265-1270, 2004.

66. Agricola E, Bove T, Oppizzi M, et al.: "Ultrasound comet-tail images": a marker of pulmonary edema: a comparative study with wedge pressure and extravascular lung water. Chest. 127:1690-1695, 2005.

67. Agricola E, Picano E, Oppizzi M, et al.: Assessment of stress-induced pulmonary interstitial edema by chest ultrasound during exercise echocardiography and its correlation with left ventricular function. J Am Soc Echocardiogr. 19:457-463, 2006.

68. Gargani L, Frassi F, Soldati G, et al.: Ultrasound lung comets for the differential diagnosis of acute cardiogenic dyspnoea: a comparison with natriuretic peptides. Eur J Heart Fail. 10:70-77, 2008.

69. Santos TM, Franci D, Coutinho CM, et al.: A simplified ultrasound-based edema score to assess lung injury and clinical severity in septic patients. Am J Emerg Med. 31:1656-1660, 2013.

70. Shyamsundar M, Attwood B, Keating L, et al.: Clinical review: the role of ultrasound in estimating extra-vascular lung water. Crit Care. 17:237, 2013.

71. Caltabeloti F, Monsel A, Arbelot C, et al.: Early fluid loading in acute respiratory distress syndrome with septic shock deteriorates lung aeration without impairing arterial oxygenation: a lung ultrasound observational study. Crit Care. 18:R91, 2014.

72. Noble VE, Murray AF, Capp R, et al.: Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. Chest. 135:1433-1439, 2009.

73. Trezzi M, Torzillo D, Ceriani E, et al.: Lung ultrasonography for the assessment of rapid extravascular water variation: evidence from hemodialysis patients. Intern Emerg Med. 8:409-415, 2013.

74. Lichtenstein DA: BLUE-protocol and FALLS-protocol: two applications of lung ultrasound in the critically ill. Chest. 147:1659-1670, 2015.

75. Ang SH, Andrus P: Lung ultrasound in the management of acute decompensated heart failure. Curr Cardiol Rev. 8:123-136, 2012.

76. Alsaddique A, Royse AG, Royse CF, et al.: Repeated Monitoring With Transthoracic Echocardiography and Lung Ultrasound After Cardiac Surgery: Feasibility and Impact on Diagnosis. J Cardiothorac Vasc Anesth. 30:406-412, 2016.

77. Díaz-Gómez J, Ripoll J, Ratzlaff R, et al.: Perioperative Lung Ultrasound for the Cardiothoracic Anesthesiologist: Emerging Importance and Clinical Applications. J Cardiothorac Vasc Anesth. 31:610-625, 2017.

78. Frassi F, Gargani L, Tesorio P, et al.: Prognostic value of extravascular lung water assessed with ultrasound lung comets by chest sonography in patients with dyspnea and/or chest pain. J Card Fail. 13:830-835, 2007.

79. Soummer A, Perbet S, Brisson H, et al.: Ultrasound assessment of lung aeration loss during a successful weaning trial predicts postextubation distress*. Crit Care Med. 40:2064-2072, 2012.

80. Mayo PH, Beaulieu Y, Doelken P, et al.: American College of Chest Physicians/La Societe de Reanimation de Langue Francaise statement on competence in critical care ultrasonography. Chest. 135:1050-1060, 2009.

81. Fagley RE, Haney MF, Beraud AS, et al.: Critical Care Basic Ultrasound Learning Goals for American Anesthesiology Critical Care Trainees: Recommendations from an Expert Group. Anesth Analg. 120:1041-1053, 2015.

82. Mahmood F, Matyal R, Skubas N, et al.: Perioperative Ultrasound Training in Anesthesiology: A Call to Action. Anesth Analg. 122:1794-1804, 2016.

83. Bongard FS, Matthay M, Mackersie RC, et al.: Morphologic and physiologic correlates of increased extravascular lung water. Surgery. 96:395-403, 1984.

84. Fernandez-Mondejar E, Rivera-Fernandez R, Garcia-Delgado M, et al.: Small increases in extravascular lung water are accurately detected by transpulmonary thermodilution. J Trauma. 59:1420-1423; discussion 1424, 2005.

85. Brown LM, Calfee CS, Howard JP, et al.: Comparison of thermodilution measured extravascular lung water with chest radiographic assessment of pulmonary oedema in patients with acute lung injury. Ann Intensive Care. 3:25, 2013.

86. Chew MS, Ihrman L, During J, et al.: Extravascular lung water index improves the diagnostic accuracy of lung injury in patients with shock. Crit Care. 16:R1, 2012.

87. Martin GS, Eaton S, Mealer M, et al.: Extravascular lung water in patients with severe sepsis: a prospective cohort study. Crit Care. 9:R74-82, 2005.

88. PiCCOplus Setup, PULSION Medical Systems, Munich, Germany, 2007.

89. Edwards Lifesciences EV1000 Clinical Platform Operator's Manual, Edwards Lifesciences, Irvine, Ca, 2011.

90. Tagami T, Kushimoto S, Tosa R, et al.: The precision of PiCCO measurements in hypothermic post-cardiac arrest patients. Anaesthesia. 67:236-243, 2012.

91. Monnet X, Persichini R, Ktari M, et al.: Precision of the transpulmonary thermodilution measurements. Crit Care. 15:R204, 2011.

92. Holm C, Mayr M, Horbrand F, et al.: Reproducibility of transpulmonary thermodilution measurements in patients with burn shock and hypothermia. J Burn Care Rehabil. 26:260-265, 2005.

93. Honore PM, Jacquet LM, Beale RJ, et al.: Effects of normothermia versus hypothermia on extravascular lung water and serum cytokines during cardiopulmonary bypass: a randomized, controlled trial. Crit Care Med. 29:1903-1909, 2001.

94. van der Heijden M, Groeneveld AB: Extravascular lung water to blood volume ratios as measures of pulmonary capillary permeability in nonseptic critically ill patients. J Crit Care. 25:16-22, 2010.

95. Groeneveld AB, Verheij J: Extravascular lung water to blood volume ratios as measures of permeability in sepsis-induced ALI/ARDS. Intensive Care Med. 32:1315-1321, 2006.

96. Monnet X, Anguel N, Osman D, et al.: Assessing pulmonary permeability by transpulmonary thermodilution allows differentiation of hydrostatic pulmonary edema from ALI/ARDS. Intens Care Med. 33:448-453, 2007.

97. Easley RB, Mulreany DG, Lancaster CT, et al.: Redistribution of pulmonary blood flow impacts thermodilution-based extravascular lung water measurements in a model of acute lung injury. Anesthesiology. 111:1065-1074, 2009.

98. Roch A, Michelet P, Lambert D, et al.: Accuracy of the double indicator method for measurement of extravascular lung water depends on the type of acute lung injury. Crit Care Med. 32:811-817, 2004.

99. Schreiber T, Hüter L, Schwarzkopf K, et al.: Lung perfusion affects preload assessment and lung water calculation with the transpulmonary double indicator method. Intens Care Med. 27:1814-1818, 2001.

100. Hedenstierna G, White FC, Mazzone R, et al.: Redistribution of pulmonary blood flow in the dog with PEEP ventilation. J Appl Physiol Respir Environ Exerc Physiol. 46:278-287, 1979.

101. Carlile PV, Hagan SF, Gray BA: Perfusion distribution and lung thermal volume in canine hydrochloric acid aspiration. J Appl Physiol. 65:750-759, 1985.

102. Kirov M, Kuzkov V, Fernandez-Mondejar E, et al.: Measuring extravascular lung water: animals and humans are not the same. Crit Care. 10:415, 2006.

103. Naidu B, Dronavalli V, Rajesh P: Measuring lung water following major lung resection. Interactive Cardiovascular & Thoracic Surgery. 8:503-506, 2009.

104. Blomqvist H, Wickerts CJ, Rosblad PG: Effects of pleural fluid and positive end-expiratory pressure on the measurement of extravascular lung water by the double-indicator dilution technique. Acta Anaesthesiol Scand. 35:578-583, 1991.

105. Saugel B, Phillip V, Ernesti C, et al.: Impact of large-volume thoracentesis on transpulmonary thermodilution–derived extravascular lung water in medical intensive care unit patients. J Crit Care. 28:196-201, 2013.

106. Deeren DH, Dits H, Daelemans R, et al.: Effect of pleural fluid on the measurement of extravascular lung water by single transpulmonary thermodilution. Clinical Intensive Care. 15:119-122, 2004.