



Extravascular lung water measurements in acute respiratory distress syndrome: why, how, and when?

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Purpose of review

Increase in pulmonary vascular permeability accompanied with accumulation of excess extravascular lung water (EVLW) is the hallmark of acute respiratory distress syndrome (ARDS). Currently, EVLW and pulmonary vascular permeability index (PVPI) can be quantitatively measured using the transpulmonary thermodilution (TPTD) technique. We will clarify why, how, and when EVLW and PVPI measurements should be performed.

Recent findings

Although the Berlin criteria of ARDS are simple and widely used, several criticisms of them have been published. The last 2 decades have witnessed the introduction and evolution of the TPTD technique for measuring EVLW and PVPI. Several publications have recommended to evaluate EVLW and the PVPI during the treatment of critically ill patients. Accurate and objective diagnoses can be made for ARDS patients using EVLW and PVPI. EVLW more than 10 ml/kg is a reasonable criterion for pulmonary edema, and EVLW more than 15 ml/kg for a severe condition. In addition to EVLW more than 10 mL/kg, PVPI more than three suggests increased vascular permeability (i.e., ARDS), and PVPI less than 2 represent normal vascular permeability (i.e., cardiogenic pulmonary edema).

Summary

EVLW and PVPI measurement will open the door to future ARDS clinical practice and research, and have potential to be included in the future ARDS definition.

Keywords

acute respiratory distress syndrome, Berlin definition, pulmonary edema, pulmonary permeability, transpulmonary thermodilution

INTRODUCTION

Pulmonary edema is one of the most common complications and health burdens in critically ill patients [1,2]. Several recent reports have found that mortality reaches up to approximately 12% for cardiogenic [3] and 30% [1] for noncardiogenic pulmonary edema, the two major forms of this condition [1,2,4]. An increase in the pulmonary capillary hydrostatic pressure (usually paralleling an increase in blood volume in the pulmonary vessels) is the main determinant of cardiogenic (or hydrostatic) pulmonary edema. Typical causes include congestive heart failure due to left ventricular failure, fluid overload caused by inappropriate fluid infusion, and untreated renal failure. On the other hand, an increase in pulmonary capillary permeability (i.e., leaky lungs secondary to inflammatory mediators) is the hallmark of acute respiratory distress syndrome (ARDS), a representative type of noncardiogenic pulmonary edema [1,2,4].

A pair of human lungs contains about 700 million alveoli, with overall superficial area approximately 100 m² (i.e., as large as half of a tennis court) [5]. The alveoli consist of an epithelial layer,

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Curr Opin Crit Care 2018, 24:209–215

DOI:10.1097/MCC.0000000000000503

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KEY POINTS

- Pulmonary edema, whether cardiogenic or noncardiogenic, is characterized by excessive accumulation EVLW; however, it is difficult to evaluate it quantitatively by radiographic findings.
- Increase in pulmonary vascular permeability is the hallmark of ARDS.
- EVLW and PVPI can be quantitatively measured by the TPTD technique.
- EVLW more than 10 ml/kg is a reasonable criterion for pulmonary edema and EVLW more than 15 ml/kg for a high degree of severity.
- In addition to EVLW more than 10 ml/kg, PVPI more than three suggests increased vascular permeability (i.e., ARDS), and PVPI less than two represent normal vascular permeability (i.e., cardiogenic pulmonary edema).

interstitium, and capillaries. The space outside the capillaries is known as the extravascular lung space. Correspondingly, the fluid in the alveoli and interstitium is called extravascular lung water (EVLW). Pulmonary edema, whether cardiogenic or noncardiogenic, is characterized by an increase in EVLW [5]. Regardless of the cause, this EVLW accumulation impairs respiratory gas exchange, resulting in respiratory distress [6].

However, it is often difficult to evaluate pulmonary edema quantitatively in terms of severity and type of disease (cardiogenic versus increased permeability), especially in severely ill patients with multiple complications and extensive medical histories [2]. In this article, we will review recent published papers and clarify why, how, and when EVLW measurements should be performed, especially in ARDS. In addition, we will suggest the quantitative diagnostic framework for evaluating pulmonary edema.

WHY IS THERE A NEED TO EVALUATE EXTRAVASCULAR LUNG WATER AND PULMONARY PERMEABILITY QUANTITATIVELY?

The existence and severity of pulmonary edema are generally evaluated based on physical examination, patient history, laboratory examination, and chest radiographic findings [2]. However, the interpretation of these parameters, including chest X ray, is often affected by subjective factors that may cause interobserver error, even among experts [2,7,8⁹]. Objective diagnosis of pulmonary edema

can be made if EVLW is evaluated quantitatively at the bedside using the transpulmonary thermodilution (TPTD) technique [1,10] (Fig. 1).

Following the first description by Ashbaugh *et al.* in 1967 [4], the definition of ARDS was continuously reworked until the publication of the American-European Consensus Conference (AECC) definition in 1994 [11]. The currently used Berlin definition was published in 2012, after minor revision from AECC definition [12]. It has been shown to have only slightly better predictive validity for mortality than the AECC definition [12]. Both the AECC and the Berlin definitions basically consist of four main components: (1) onset (acute), (2) chest radiography findings, (3) arterial blood gas results (PaO₂/FiO₂ ratio), and (4) absence of cardiogenic pulmonary edema [11,12].

Although the Berlin criteria are simple and widely used, significant criticisms of them have been published. First, accurate interpretation of chest radiography is required for the diagnosis. In a supplemental publication of the Berlin definition [13], expert panels (the ARDS Definition Task Force) presented typical examples of 12 chest radiographs, which were categorized into three groups: consistent with, inconsistent with, and equivocal for ARDS. However, the interpretation of chest radiography is often complicated and lacking in objectivity. Sjoding *et al.* [9¹⁰] recently reported that clinicians showed only moderate interobserver agreement when diagnosing ARDS in patients with hypoxic respiratory failure according to the Berlin criteria. This result was driven primarily by the low reliability of the interpretation of chest images [9¹⁰]. This conclusion was supported by a recent multicenter prospective study of interrater agreement, in which 286 intensivists independently reviewed the same 12 chest radiographs developed by the panels, before and after training. Radiographic diagnostic accuracy and interrater agreement were found to be poor when the Berlin radiographic definition was used and were not significantly improved by the training set of chest radiographs developed by the Task Force [8¹¹].

Second, although the severity of ARDS is determined by the PaO₂/FiO₂ ratio (i.e., mild, moderate, and severe ARDS for PaO₂/FiO₂ of 200–300, 100–200, and, < 100, respectively), this ratio depends strongly on FiO₂, and the relationship between the numerator and denominator has been reported to be nonlinear [14]. In addition, the level of positive end-expiratory pressure (PEEP) significantly impacts this ratio [15].

Third, the absence of cardiogenic pulmonary edema may not be an essential prerequisite for increased permeability pulmonary edema. Increased pulmonary permeability is the hallmark, but is not

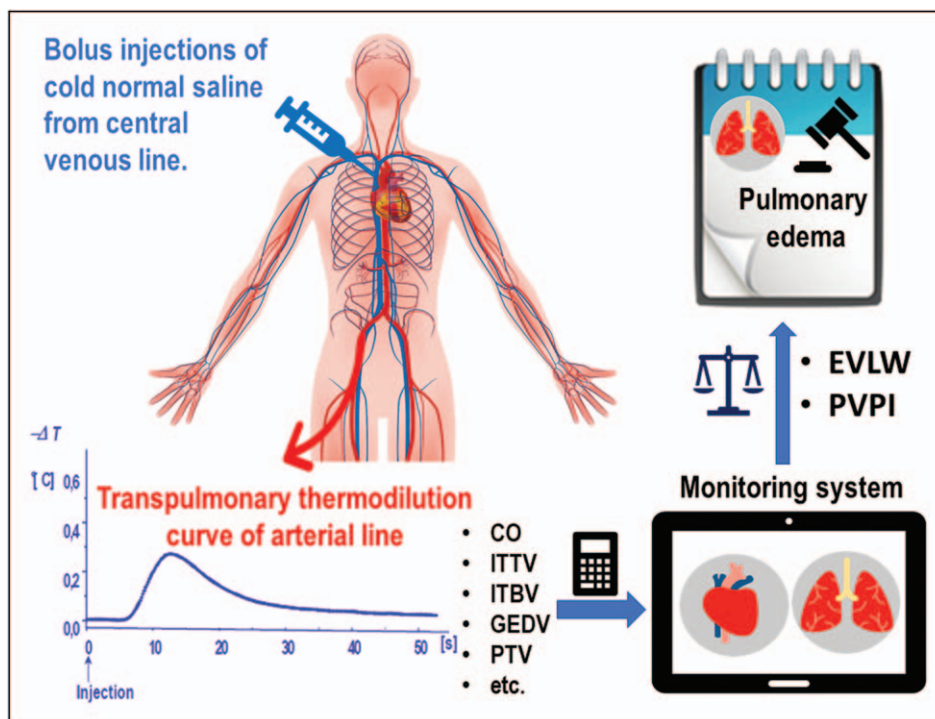


FIGURE 1. Estimation of extravascular lung water and pulmonary permeability index by TPTD method. TPTD method requires the injection of a 15–20 ml bolus of cold ($<8^{\circ}\text{C}$), isotonic saline through the central venous catheter. A mean value of at least three cold bolus injections reaches acceptable precision in clinical practice. The thermodilution curves are then recorded by the thermistor at the tip of the arterial catheter to allow for an estimation of the cardiac output (CO) using the Stewart–Hamilton method. Concurrently, the mean transit time and the exponential downslope time of the TPTD curve are calculated. The product of the CO and the mean transit time represents the intrathoracic thermal volume (ITTV). The product of the CO and the exponential downslope time represents the pulmonary thermal volume (PTV). GEDV is calculated as the difference between the ITTV and PTV, and represents the combined end-diastolic volumes of the four cardiac chambers. This allows for the calculation of the intrathoracic blood volume (ITBV) from its linear relationship with GEDV: $\text{ITBV} = [1.25 \times \text{GEDV}] - 28.4$. EVLW is the difference between the ITTV and the ITBV. The pulmonary blood volume is deducted from the difference between the PTV and the EVLW. The PVPI is calculated as the ratio between the EVLW and the pulmonary blood volume. Explanations mostly reproduced from [10]. TPTD, transpulmonary thermodilution.

the only cause of accumulation of EVLW in ARDS. Patients with abnormal cardiac function may also have leaky lungs at the same time. For example, patients with a history of chronic cardiac disease and reduced cardiac function may develop abdominal sepsis due to bacterial peritonitis, and then increased lung permeability secondary to the generation of inflammatory mediators.

Finally, and most importantly, studies have shown only modest agreement between the pathological findings for ARDS (primarily diffuse alveolar damage; DAD), and the AECC diagnostic criteria [16–19]. Even after the revision of the Berlin criteria, a recent autopsy study found that histopathologic findings of DAD were observed in only 45% of patients identified as having ARDS [20]. This means that more than half of the patients were suffering from a wide range of respiratory failure symptoms without having DAD [7].

Therefore, there is also a need to evaluate pathophysiological hallmarks of the disease, pulmonary vascular permeability, for the diagnosis of the ARDS. Pulmonary vascular permeability index (PVPI) can be measured using the TPTD technique along with EVLW [1,21]. This information may help in assessing the severity of the disease and distinguishing the two types of pulmonary edema quantitatively, which may guide the selection of the correct therapeutic strategy [7].

HOW TO MEASURE EXCESS EXTRAVASCULAR LUNG WATER AND PULMONARY VASCULAR PERMEABILITY INDEX

The last 2 decades have witnessed the introduction and evolution of the TPTD technique for measuring EVLW and PVPI in a clinical setting. Currently,

there are two similar commercially available TPTD systems, the PiCCO monitoring system [ProAQT platform or PiCCO2 monitoring (Pulsion/Getinge Medical Systems, Munich, Germany)] [10] and the EV1000 system (VolumeView, Edwards Lifesciences, Irvine, California, USA) [22]. Both systems require a central venous catheter and a thermistor-tipped arterial catheter. After injection of 15 ml of cold isotonic saline into the central venous catheter, the arterial catheter detects thermodilutional changes, which allow for estimation of cardiac output, global end-diastolic volume (GEDV), global ejection fraction, EVLW, and PVPI (Fig. 1). The two devices (i.e., PiCCO or EV1000) measure almost the same sets of hemodynamic and pulmonary variables, including EVLW and PVPI. Although the details of the algorithms used by the proprietary software packages for the systems are not fully open to public, both work on generally the same principles. However, the PiCCO manufacturer frequently updates and revises their algorithm and software based on the results of published validation studies [23–25].

The accuracy of EVLW measurement by the PiCCO system was first validated against gold standard gravimetric measurement in animal models [26]. Thermodilution measurement of EVLW values showed high accuracy in normal lungs, cardiogenic pulmonary edema, and ARDS models. In a human autopsy study, we observed a definite correlation between EVLW and postmortem lung weight from a wide range of normal and injured lungs [10]. A recent study of brain-dead patients before organ transplantation suggested a close correlation between thermodilution EVLW and gravimetry EVLW [27].

Until recently, the reliability of the EVLW value among patients with impaired cardiac function and valvular disorders was only validated to a limited degree. Hilty *et al.* [28^{***}] evaluated patients undergoing elective left and right heart catheterization, along with left ventricular angiography. They found that TPTD measurement of blood flow was unaffected by differences in ventricular size and outflow obstruction.

WHEN TO EVALUATE EXTRAVASCULAR LUNG WATER AND PULMONARY VASCULAR PERMEABILITY INDEX

Several publications, and many experts in this field, recommend TPTD to evaluate EVLW and the PVPI during the treatment of critically ill patients [29]. Accurate and objective diagnoses can be made for ARDS patients using EVLW and PVPI.

Several studies suggest that a normal EVLW value should be approximately 7 ml/kg and should not exceed 10 ml/kg (indexed by predicted body weight). Our clinical–pathological study showed mean EVLW values of approximately 7.3 ± 2.8 ml/kg to be the normal reference range for humans ($n = 534$) [10]. This value was supported by Eichhorn *et al.* [30], who published a meta-analysis of clinical studies ($n = 687$) in which they found a mean EVLW of 7.3 ml/kg (95% confidence interval, 6.8–7.6) in patients undergoing elective surgery, who were not supposed to have pulmonary edema. More recently, Wolf *et al.* [31] obtained a similar result (8 ml/kg, interquartile range 7–9) in 101 elective brain tumor surgery patients.

In addition, Japanese nation-wide autopsy data ($n = 1688$) indicated that an EVLW more than 9.8 ml/kg represented the optimal discrimination threshold for a diagnosis of pulmonary edema from normal lungs, and an EVLW level of 14.6 ml/kg represents a 99% positive predictive value [32]. The landmark study by Sakka *et al.* [33] showed that the degree of initial EVLW on admission to the intensive care unit correlated with mortality, with a significant cut-off point of 14 ml/kg. The relationship between EVLW and prognosis was also clearly demonstrated in a systematic review of literature [34] and a recent large scales study [35].

The results of our multicenter study from Japan of 192 ARDS patients suggested that delta-EVLW (the decrease in EVLW during the first 48 h) was associated with 28-day survival in ARDS [36]. Moreover, a recent retrospective study from China also found that the daily maximum values of EVLW in the 48 h after initial resuscitation were independent predictors of 28-day mortality in septic shock patients [37]. With a cutoff value of 12.5 mL/kg, the daily maximum values of EVLW in septic shock patients after initial resuscitation were associated with a more positive fluid balance and increased mortality [37]. Therefore, not only is the initial absolute value of EVLW useful for diagnosis of ARDS, but subsequent changes must also be taken into consideration in clinical practice [36].

Several experts have proposed that, based on the evidence, EVLW more than 10 ml/kg is a key criterion to include in a future definition of ARDS [38]. According to pathological [32] and clinical [33] studies, EVLW values above 10 ml/kg represent higher than normal EVLW, and 15 ml/kg may be the key number to remember for severe pulmonary edema. By evaluating EVLW, we can (objectively at the bedside) accurately assess the initial severity of pulmonary edema as well as subsequent changes, thereby monitoring the ongoing therapeutic strategy.

We must always consider lung vascular permeability in addition to EVLW when we diagnose the cause of pulmonary edema, particularly with regard to fluid management. Giving fluids to a patient with high vascular permeability might result in very severe accumulation of EVLW [39]. PVPI can be calculated from the relationship between EVLW and pulmonary blood volume. If the EVLW is elevated without increase in PVPI, the patient has cardiogenic pulmonary edema. On the other hand, an increase in EVLW along with an increase in PVPI means that the patient has increased permeability pulmonary edema.

Groeneveld and Verheij [40] demonstrated that lung vascular injury is associated with a rise in PVPI in mechanically ventilated patients with pneumonia or extrapulmonary sepsis-induced ARDS. Monnet *et al.* [41] showed that PVPI allows differentiating hydrostatic pulmonary edema from increased permeability pulmonary edema, with a cut-off PVPI value of 3. A large-scale prospective multicenter study from Japan found almost the same results, in that a PVPI cut-off value between 2.6 and 2.85 provided a definitive diagnosis of ARDS (specificity, 0.90–0.95), and a value less than 1.7 ruled out an ARDS diagnosis (specificity, 0.95) [42]. Among other recent studies that reported patients

without increased permeability pulmonary edema, PVPI was reported to be less than 2 [43] or 3 [28^{***}] in all of them. Taking all the evidence into account, PVPI less than approximately 2 may represent normal pulmonary permeability, and PVPI less than 3 indicates leaky lungs.

DIAGNOSTIC FRAMEWORK OF PULMONARY EDEMA

Synthesizing the results of the existing literature, we suggest the following diagnostic framework (Fig. 2). For diagnosing the existence of pulmonary edema, EVLW more than 10 ml/kg may be reasonable. EVLW more than 15 ml/kg indicates severe pulmonary edema. After quantitative diagnosis as pulmonary edema by EVLW more than 10 ml/kg, PVPI should be considered. PVPI less than 2 may represent normal pulmonary permeability, suggesting cardiogenic pulmonary edema. PVPI more than 3 (with EVLW > 10 ml/kg) represents increased permeability pulmonary edema, or ARDS. PVPI more than 3 and EVLW more than 15 suggest severe ARDS. Even if the initial EVLW and PVPI are high and indicate a high probability of mortality, if the values improve over time (especially during the first 48 h), a better outcome can be expected.

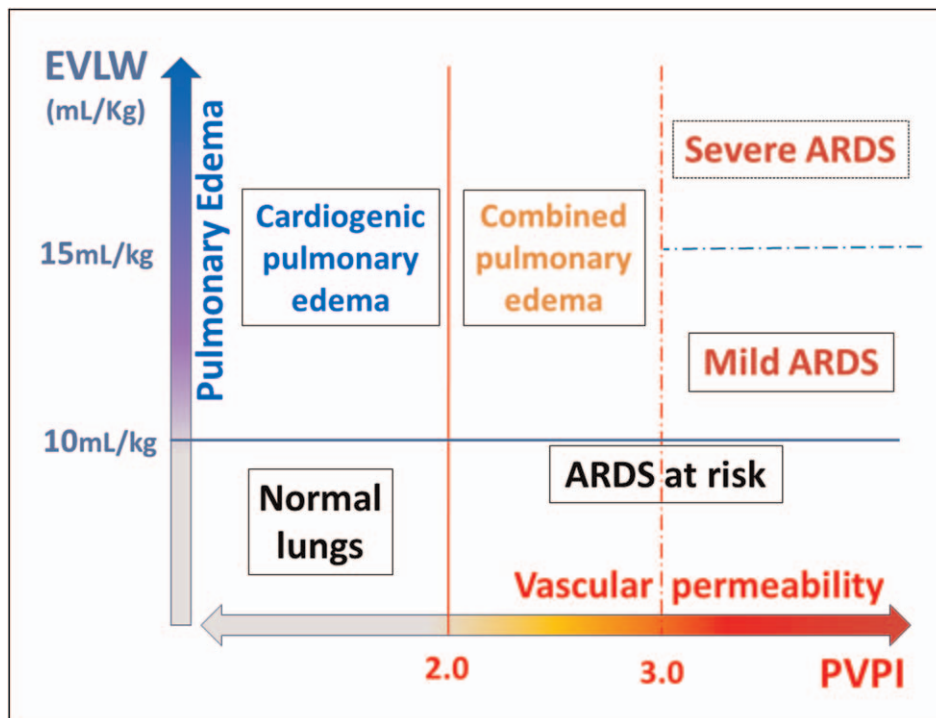


FIGURE 2. Diagnostic framework for pulmonary edema. Pulmonary edema: EVLW more than 10 ml/kg. Cardiogenic pulmonary edema: EVLW more than 10 ml/kg and PVPI less than 2.0. ARDS: EVLW more than 10 ml/kg and PVPI more than 3.0. Combined pulmonary edema (e.g., cardiogenic pulmonary edema, reduced cardiac function or fluid overload, and permeability lung injury secondary to the generation of inflammatory mediators): EVLW more than 10 ml/kg and PVPI of 2.0–3.0.

CLINICAL USE OF EXTRAVASCULAR LUNG WATER AND PULMONARY VASCULAR PERMEABILITY INDEX FOR EVALUATING ARDS AND OTHER DISEASES

There are many recent studies evaluating EVLW/PVPI in the field of ARDS research, from all over the world [44,45[■]]. For example, a recent study evaluated potential treatments for ARDS, including recruitment maneuvers [45[■]]. Currently, EVLW/PVPI evaluation is not restricted to patients with pulmonary edema, sepsis/septic shock, and pancreatitis, it is also expanding to other conditions, such as burns [46[■],47], lung surgery (endarterectomy [48[■]] or lung transplant [49] [50[■]]), and postcardiac arrest syndrome [51]. The clinical indications for measuring EVLW and PVPI may thus be expanding.

LIMITATIONS OF TRANSPULMONARY THERMODILUTION

TPTD has several limitations, mainly vascular obstruction and focal lung injury, which clinicians must bear in mind when interpreting the data. The amount of EVLW, the PaO₂/FIO₂ ratio, the tidal volume, and the PEEP level may affect the estimation of EVLW [21,52]. Although there has been a concern that the use of extracorporeal lung support may interfere with the accuracy and precision of the measurements, this support with a single-site jugular double-lumen cannula did not interfere with hemodynamic monitoring measurements using the TPTD method in ARDS patients [53]. Other limitations are discussed elsewhere in detail [21,52].

CONCLUSIONS

EVLW and PVPI can be used to quantitatively establish the existence, evaluate the severity, and identify the nature of ARDS. EVLW-based criteria have been validated in several clinical and pathological studies: EVLW more than 10 ml/kg is a reasonable criterion for pulmonary edema, and EVLW more than 15 ml/kg for a high degree of severity. PVPI less than 2 may represent normal pulmonary permeability, and PVPI more than 3 suggests leaky lungs. These values of EVLW and PVPI have the potential to be included in the future definition of ARDS. EVLW and PVPI measurements will open the door to future ARDS clinical practice and research.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

Disclosure: Dr Tagami is a member of the Medical Advisory Board of Pulsion Medical system. Dr. Ong has no conflict of interest to declare regarding this study.

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