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Review Article

Methods for Qualitative and Quantitative Assessment of Extravascular Lung Water–Clinical Application, Advantages, and Disadvantages

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ABSTRACT

Background: Lung edema is a life-threatening condition associated with prolonged intensive care unit stay and high mortality. The increased extravascular lung water (EVLW) causes impaired lung compliance and refractory hypoxemia. Although there are promising methods for the detection of EVLW, there is not yet a universally accepted one, and a systematic approach to the problem is missing. The discussion in this article is on the potential of the described assessment methods and techniques and reveals the strong and weak points according to their practical application.
Methods: The discussion in this article is on the potential of the described assessment methods and techniques. According to our comparative analysis, the strong and weak points regarding their practical application are presented in a table.
Results: This review article summerizes advantages and disadvantages of the most common methods in clinical practice.
Conclusion: Although there are promising methods for the detection of EVLW, there is not yet a universally accepted one, and a systematic approach to the problem is yet to be found.

Introduction

The amount of extravascular lung water (EVLW) is a determining factor for the clinical outcome in patients with ARDS [1].

Physiologically EVLW is considered to be around 500 ml [2] or 7 ml/kg predicted body weight [3]. Its amount depends on the balance between these forces:

$$EVLW = (L_p x S)((P_c - P_i) - k(\Pi_c - \Pi_i)) - \text{Lymph flow [4]}$$

where EVLW=extravascular lung water (ml), Lp=the hydraulic conductivity for water (cm/min/mmHg), S=surface area (cm^2), Pc and Pi=the hydrostatic pressure within the capillary and interstitial spaces, respectively (mmHg), s=the reflection coefficient for protein (no units), and Pc and Pi=the oncotic pressure within the capillary and interstitial spaces (mmHg).

Dysregulation in the balance of these forces causes abnormal elevation of EVLW, clinically presented as pulmonary edema [5].

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An approach for the estimation of the EVLW must be found for practice: it should be informative about the development of pulmonary edema before clinical manifestation. The ideal test should be accurate, sensitive, repeatable, comparative, noninvasive, practical and inexpensive [6].

Methods

Imaging methods

What is common in all imaging methods is that they are informative for the volume and spatial processes [4]. Every picture (pixel) or volume (voxel) element in a cross-sectional image of the lung represents a specific volume [4]. So, the variability of the image depends on the concentration (for example, ml EVLW/ml lung). Since the lung is an air-containing structure, the amount of parenchyma within each voxel can change depending on the underlying state of lung inflation (lung volume) [4]. To quantify EVLW, the signal from the entire organ should be investigated. Even though the specificity is different, no imaging method (except the positron emission tomography) cannot estimate quantitatively the amount of EVLW, but they all give information about the total water content (intravascular and extravascular) [4] (Table 1).

Table 1- compare advantages and disadvantages of available methods in estimating EVLW from practical point of view

Method	Advantages	Disadvantages	References
Gravimetry	-referent for EVLW measurement -low price	-can be applied only in autopsy	[7-8]
Chest radiography	-easy applied in practice -can be done next to the patient's bed -noninvasive -gives information about possible etiology -repeatable -non expensive	-non quantitative method -relative subjectivity of the method -depends on the technical setting: equipment quality; preexposition; rotation/ posture of the patient, appliance of PEEP - depends on the clinical experience of the doctor who reads the chest xray -no sensitivity about small changes in the amount of EVLW	[9–11]
Computed tomography (CT)	-detailed information for structural changes -correlates with local pulmonary edema -noninvasive	- cannot be applied next to the patient's bed - cannot be applied for routine, repeatable investigations -relatively high doses of ionising radiation -expensive	[4,12]
Magnetic resonance imaging (MRI)	-high image credibility -no radiation during the investigation -comparable -noninvasive	-inability to be done next to the patient's bed -sensitive to the cardiac and respiratory movements -long duration of the investigation -cannot be applied for routine investigation of critically ill patients -high cost	[4,8,13]
Positron emission tomography (PET)	-precise in measurement of EVLW	-radioactive markers are used -not appliable for routine use -expensive -difficult access	[14]
Electrical impedance tomography (EIT)	-noninvasive -easy to be applied next to the patient's bed -repeatable -informative for ventilation features - non expensive	- it is not in the routine practice -missing protocols for proper position of the belt -non quantitative -cannot be applied whe there is chest bandage	[15-16]
Lung ultrasound (LUS)	-no radiation -repeatable -can be applied next to the patient's bed -quick access	-depends on the examinator experience -not appliable in chest trauma, obese patients, subcutaneous emphysema -Not quantitative test - contamination possibility	[17–21]

	- non expensive -informative for other pathologies		
Double indicator dilution method	-quantitative method -good correlation compared with the gravimetry - repeatable -applied next to the patient's bed	-invasive method -practically slow and difficult to be applied routinely -used dye could have impaired clearance in patients with compromised liver function -relatively expensive	[22]
Transpulmonary termodilution method (TPTD)	-quantitative method -good correlation with double indicator method and gravimetry -repeatable -mini-invasive -can be applied next to the patient's bed -no radiation or dye needed	- Mini invasive method - limitations: lung resection, massive obstruction of pulmonary vessel, high PEEP (above 15), continuous renal replacement therapy	[23–25]

Chest radiography (X-ray)

This is the most used imaging method in practice [26]. It provides information about the presence of pulmonary edema, the overall distribution, and the possible etiology. The EVLW should be increased by at least 30% [27] in order to detect some of the characteristic features: pulmonary congestion, peribronchial "cuffing," perihilar "haze," Kerley's line, and the interstitial pattern of the radiographic patterns. As EVLW increases, the radiographic densities occupy a greater fraction of the total lung airspace; as edema worsens, densities become more and more "white" [6].

Research by Saugel et al. [28] on 71 patients confirms only 55% diagnostic accuracy in recognition of increased levels of EVLW. This fact proves that chest X-ray is not suitable for early recognition and estimation of pulmonary edema [8].

Computed tomography (CT)

Computed tomography is based on differential attenuation of X-ray absorption for cross-sectional imaging of the thorax and subsequent regional assessment of lung pathologies [26]. It provides detailed information about the type of pulmonary pathologies, including airway processes, interstitial ones, and thromboembolic incidents [26]. The main advantage of using CT over conventional radiography concerning EVLW measurement is that the density of the infiltrates can be determined quantitatively [4]. Also, during the transverse section, the spatial distribution of the edema can be detected [4]. Measurement of the density of the process can identify when EVLW is elevated by 50% (experimental animal study) [12].

In a research study, Leiser et al. [29] establish the ELW index (excess lung weight), which is achieved after manual segmentation and calculations of the lung CT scan. The index is compared with EVLW delivered from transpulmonary thermodilution, SOFA score, and oxygenation index, and there is a strong correlation [29]. This maneuver is time-consuming and specific and is not applicable in everyday practice.

Magnetic resonance imaging (MRI)

Technical development in the recent years allows a wide range of diagnostic options using MRI in pulmonary investigation: regional ventilation, perfusion, perfusion/ventilation mismatch, diffusion, and lung water estimation [30]. The estimation of EVLW is based on the ability to align hydrogen nuclei (protons) of water in the direction of an externally applied magnetic field. When the patient lies in a magnetic field being radiated with electromagnetic radiation, a resonance develops from the absorption and the consequent release of energy as the pulse is applied and then discontinued. This energy can be detected by properly placed amplifiers, producing signals with different strengths, varying according to the strength of the magnetic field and the frequency of the radio frequency pulse. The spin echo sequence is the only one to this moment to measure extravascular lung water [4]. A lot of studies report a good correlation between EVLW measured by MRI and the values measured by the gold standard—gravimetric method [31–35].

A big advantage is the absence of ionizing radiation for the measurements [13]. An issue to consider is that normal to mildly edematous lungs produce weak signals, and MRI can underestimate true lung water content in 2-4% of the cases [34, 36]. Due to the method's limitations, at this point MRI is more suitable for research-based applications of measuring EVLW than for clinical use. Also, most of the techniques used to date cannot differentiate intravascular lung water from extravascular lung water, complicating interpretation when pulmonary blood volumes are not constant. The practical application of MRI measurement of EVLW depends mainly on developing rapid and convenient techniques.

Lung ultrasound

An excellent diagnostic potential of lung ultrasound is presented by Lichtenstein et al. [37]. This method is reliable in diagnosing a variety of lung diseases: pleural effusion [38], parenchymal consolidation [39], and pneumothorax [40-41]. The presence of B lines is significant for diagnosing lung edema [42]. They are visualized as hyperechogenic artifacts, falling down from the pleural line, well outlined, synchronically moving with the respiratory movements [42]. If more than two B lines are visualized in an intercostal space, this is considered a diagnostic marker for interstitial syndrome [42]. Lung ultrasound technique has several advantages as a diagnostic tool: it is noninvasive, applicable next to the patient's bed, and repeatable [37]. With the admission of the new ARDS definition, it is expected for wider incorporation of this method in clinical practice.

Positron emission tomography (PET)

This is a nuclear medicine imaging technique that uses radioactively labeled positron-emitting isotope tracers, and by tracing them, lung water can be measured. The tracers are administered separately (intravenously and inhalationally) to distribute between the total and intravascular spaces of the lung. The emissions of these tracers are detected and reconstructed to form an image. PET scanner is considered a reliable standard of measuring EVLW because the tomographic image can be created and normalized for the attenuation of the structure being imaged using a transmission scan [43].

EVLW measurements by PET scan have good correlation with the gravimetric measured ones ($r = 0.86$–0.93) [44–45]. PET scan measurements have a high degree of reproducibility, as the coefficient of variations in the second measurement is $<5\%$ [44]. The method shows exquisite sensitivity—as little as 1 ml of additional extravascular water can be detected [4, 44].

Electrical impedance tomography (EIT)

The impedance technique is a noninvasive, non-radiational imaging method for personalized monitoring a range of lung function parameters, including functional residual capacity, regional ventilation, and perfusion [46]. This method can be applied next to the patient's bed [4, 15]. Measurement of lung water is based on the principle that air and fluid have different resistance to current flow. As intrathoracic water increases, electrical conductance across lungs improves and impedance decreases [47]. Although it is a measure of total pulmonary fluid rather than a direct measure of EVLW, Kunst et al. [48] demonstrate a strong correlation between measured EVLW by EIT and the thermal dye dilution technique. A new parameter, Lung Water Ratio (LWREIT) is established [49].

EVLW occupies the dependent parts of the lung, and the ventilation is in nondependent ones. These changes can be monitored by EIT. The body position also could cause gravity connected with redistribution of extravascular water and ventilatory changes, which can be reported. These ventilatory changes due to the body position determine EVLW and other fluid processes in the lung, for they could not change the ventilation after the change in the body position. This is how LWREIT is determined. In an animal model study, Trepte et al. [49] show good correlation between LWREIT proved pulmonary edema and the measured one by gravimetry method. LWREIT itself cannot assure quantitative information for pulmonary edema.

Indicator Dilution techniques

The double colorimetric thermodilutional method (TTD) consists of the injection of cold serum and an indicator (protein-bound coloring agent). It is considered that the thermoindicator will diffuse and fulfill the whole intrathoracic compartment, and the dye indicator will remain in the intravascular compartment. The difference in the volume of distribution is equal to EVLW [50]. This method is used in clinical practice, as Eisenberg et al. [51] prove that managed fluid therapy according to the values of EVLW affects the patient's outcome.

Nevertheless, the potential [52] of the method is slow for routine practice. Still, this method is important for investigating EVLW abilities and is fundamental for the development of the transpulmonary thermodilution technique [50].

Transpulmonary thermodilution (TPTD)

Widely validated method for EVLW measurement is PICCO—thermodilution technique, based on the Steward Hamilton principle [23]. It is considered a minimally invasive method, as cannulation of the central vein and peripheral artery is only needed [53]. Cold serum is used as a thermal indicator [53].

The TPTD technique is validated by comparing results measured by the double colorimetric thermodilutional method [23], by the gravimetric method in animals [54-55], and by gravimetry in people [56]. Tagami et al. [56] in an autopsy study prove a strong correlation coefficient of 0.90 in EVLW measurement between TPTD and gravimetry. Via TPTD, it is possible to establish even a small elevation of EVLW, as after bronchoalveolar lavage [57]. Tagami et al. [58] label EVLW as "the bridge between pathology and clinical manifestation of ARDS."

High values of EVLW are associated with the severity of lung injury [59]. TPTD via PICCO monitoring provides detailed hemodynamic monitoring. EVLW and its dynamic changes have strong prognostic value for intensive care stay and mortality [60]. Moreover, EVLW is considered a helpful marker in the evaluation and guidance of the infusion strategy [61-64]. No serious complications are not being reported [65].

A change in the EVLW values during the first 48 hours is associated with 28-day survival [66]. EVLW changes represent the pathophysiological status of ARDS development. A systemic approach should be accepted for early recognition and evaluation of EVLW. In general, all the imaging methods present with limitations, affecting the accuracy or the range of application. TPTD measured EVLW over consecutive days is a quantitative and sensitive method and can provide rapid and sensitive information at the bedside. The benefit of detecting elevation of EVLW is applying early goal directed treatment.

Results

A detailed discussion of the advantages and disadvantages of the most common methods in clinical practice for estimation of EVLW was performed. Since imaging methods so far are the most used in clinical practice for estimation of the edema, the last decades TPTD takes advantage in the routine clinical practice. EVLW is undoubtedly a prognostic marker for severity, mortality and prognosis of ARDS and its values are of immense importance, regarding treatment behaviour.

Conclusion

There are several diagnostic approaches to measuring EVLW, validated against the gold standard—gravimetry. Each technique varies in its strong and weak features, also in practical accessibility. EVLW has the potential to be valuable for both clinicians and researchers for optimizing and taking advances in the diagnosis of ARDS. To fulfill this potential, optimization of the existing technologies should produce improvements in accuracy, sensitivity, and reproducibility in the measures.

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