The measurement of lung water

Neale R. Lange and Daniel P. Schuster

Introduction: In this review, we compare the spectrum of currently available methods for quantifying pulmonary edema in patients.

Review: Imaging and indicator dilution techniques comprise the most common strategies for measuring lung water at the bedside. The most accurate (within 10% of the gravimetric gold standard) and most reproducible (<5% between-test variation) are also, unfortunately, the most expensive and most difficult to implement for purposes of large-scale clinical trials or for routine clinical practice.

Conclusion: The standard chest radiograph remains the best screening test for the detection of pulmonary edema. Indicator-dilution techniques are probably the best available method at present for quantitation in patient groups.

Addresses: Washington University School of Medicine, St Louis, Missouri, USA

Correspondence: Daniel P. Schuster, MD, Washington University School of Medicine, 660 South Euclid Ave., Campus Box 8225, St. Louis, MO 63110, USA. Tel: +1 314 362-3776; fax: +1 314 747-8200

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Introduction

Although about 80% of the lung is made up of water, gas-exchanging air spaces are protected by various barriers and drains. In multiple disease states, through injury or pressure (or both), these protective mechanisms fail, resulting in the abnormal accumulation of extravascular lung water (EVLW). The principle paradigm describing fluid flux in the lung is the 'Starling equation', which can be modified to account for the total surface area over which filtration might occur. 'Lymph flow' is a term summarizing those mechanisms responsible for returning extravasated fluid to the vascular compartment:

$$EVLW = (L_p \times S)\,[(P_c - P_i) - \sigma\,(\Pi_c - \Pi_i)] - \text{lymph flow} \qquad [1]$$

where EVLW = extravascular lung water (ml), L_p = the hydraulic conductivity for water (cm/min/mmHg), S = surface area (cm^2), P_c and P_i = the hydrostatic pressure within the capillary and interstitial spaces respectively (mmHg), σ = the reflection coefficient for protein (no units), and Π_c and Π_i = the oncotic pressure within the capillary and interstitial spaces (mmHg).

This equation describes the formation of interstitial edema accommodated by the interstitium. Subsequent movement of fluid into the air spaces develops by a more rapid process, termed alveolar flooding [2,3]. Normally EVLW is < 500 ml [4–7]. With alveolar flooding, lung water content is usually > 75–100% above normal [8]. It is at this point that physiologic impairment usually occurs. Thus, any method that would be clinically useful must be able to detect changes in EVLW below the threshold of alveolar edema.

Although outcome has never been shown to be linked directly to the amount, or even continued presence, of pulmonary edema *per se*, the possibility that sufficiently sensitive and accurate techniques could be used to detect pulmonary edema even before it becomes apparent clinically, or could be used to provide information about the natural history of pulmonary edema or its response to therapeutic intervention, is so inherently attractive that the effort to develop and validate such techniques still continues.

The ideal test should be accurate, sensitive, reproducible, non-invasive, practical and inexpensive [9]. There is no single ideal clinical test. Experimentally, EVLW can be evaluated and measured by histologic or gravimetric methods [10]. This comparative review focuses attention specifically on those methods, which can be clinically applied.

EVLW = extravascular lung water; PET = positron emission tomography; CT = computed tomography; NMR = nuclear magnetic resonance; ARDS = acute respiratory distress syndrome; EIT = electrical impedance tomography; ETV, extravascular thermal volume; PTV = pulmonary thermal volume; PEEP = positive end-expiratory pressure

Table 1

Clinically appropriate methods to quantify pulmonary edema

	Measures	Quantitation	Accuracy*	Reproducibility (COV)	Sensitivity†
CXR	LD	Poor	Unknown	Unknown	Moderate
CT	LD	Excellent	Unknown‡	Unknown‡	High
NMR	TLW	Fair	Underestimates by −40%§	5–10%	Poor¶
PET	EVLW	Excellent	Underestimates by 10–15%	< 5%	High
ID	EVLW	Good–excellent	Overestimates by 10–20%#	4–8%	Moderate

*None of the methods can distinguish whether an increase in extravascular lung water (EVLW) represents non-cellular pulmonary edema or cellular water from an inflammatory infiltrate. †Sensitivity to change. ‡Presumably excellent, but formal studies never performed. §The underestimates are primarily in normal or mildly edematous lungs. ¶The poor sensitivity is primarily in normal or mildly edematous lungs. #The overestimation is primarily in normal or mildly edematous lungs. TLW, total lung water (of a region on an image); LD, lung density; COV, coefficient of variation; CXR, chest X-ray; CT, computed tomography; NMR, nuclear magnetic resonance; PET, positron emission tomography; ID, indicator dilution methods.

Imaging methods

General comments

Common to all imaging methods is spatial information and physical volume. Each picture (pixel) or volume (voxel) element in a cross-sectional image of the lungs represents a specific physical volume. Thus, the units for a variable within that element are those of concentration (e.g. ml EVLW/ml lung). Since the lung is an air containing structure, the amount of lung parenchyma within each voxel can change, depending on the underlying state of lung inflation (lung volume). To quantify changes in images of EVLW in absolute terms, the signal over the entire organ must be integrated.

Most imaging methods (except positron emission tomography; PET) for evaluating pulmonary edema (Table 1) do not estimate EVLW *per se*, but instead produce estimates of total water content or concentration (i.e. vascular + extravascular water). The data from such methods can be misinterpreted if the blood volume of the lungs is not constant. Although spatially specific to varying degrees, no modality can resolve composition of edema on density alone since the edema, blood and inflammatory white cells are virtually identical, leading in general to an overestimation of EVLW *per se*. Certainly no modality can differentiate between intra- and extracellular water.

Chest radiography

A chest roentgenogram is commonly used to detect whether or not pulmonary edema is present, to describe its overall distribution within the lung, and to evaluate associated findings to infer a probable etiology. It can also be used, at least semi-quantitatively, to estimate the amount of pulmonary edema that is present as well. Several features of the chest radiograph make such an interpretation possible: (1) certain characteristic 'signs' are associated with only modest increases in EVLW (perhaps as little as 30% above normal values) [11] such as pulmonary 'congestion', vascular 'redistribution', peribronchial cuffing, perihilar 'haze', Kerley's lines, and an 'interstitial' pattern to the radiographic densities; (2) as EVLW increases, the radiographic densities occupy a greater fraction of the total lung airspace (often, mild-to-moderate amounts of edema are present in gravity-dependent lung regions only, while more severe increases in EVLW involve both dependent and non-dependent lung) [12]; and (3) as edema worsens and water displaces air in any given lung region, the 'density' of the 'infiltrate' also worsens, becoming more and more 'white'.

Although relatively quantitative and potentially informative as to etiology, accuracy (the amount of EVLW present) is significantly limited by acquisition techniques and clinical issues that override standardization procedures [13,14] (especially in the critically ill). Under clinically relevant conditions, the correlation of EVLW by chest radiography to other established techniques has been weak [15].

Computed tomography

The principle advantages of using X-ray computed tomography (CT) over conventional radiography are that the density of the infiltrates can be determined quantitatively, the spatial distribution of edema in transverse sections can be defined, and, of course, associated (and at times clinically relevant) findings can be identified. Lung density can be quantified with X-ray CT because the arbitrary Hounsfield units used for CT display can be calibrated against objects or substances of known density. Experimentally, CT-derived estimates of lung density increase by 69% when gravimetric measurements of lung weight increase by about 250% [16] (this difference in the percentage increase does not really indicate anything about accuracy since the units of measurement are not the same). CT densitometry is able to detect rather modest (~50%) increases in EVLW in experimental animals [17]. Obviously, it is not portable and involves exposure to ionizing radiation.

Nuclear magnetic resonance (NMR) imaging

Another emerging approach to estimating lung water content is based on the ability to align hydrogen nuclei (protons) of water in the direction of an externally applied magnetic field [18]. When a subject lays within a magnetic field and is then irradiated with electromagnetic radiation in the form of a correctly applied radiofrequency pulse, 'resonance' (i.e. 'nuclear magnetic resonance') develops from the absorption and subsequent release of energy as the pulse is applied and discontinued. This energy can be detected with appropriately placed amplifiers, producing a signal of varying strength, depending on the strength of the magnetic field and the frequency of the radiofrequency pulse. The spin-echo sequence is the only one to date that has been employed to measure lung water.

Signal intensity, detected after a spin-echo pulse sequence, varies as a function of the time it is sampled once the 90° radiofrequency pulse is stopped (the 'relaxation' time). Generally, proton density images have been obtained with pulse sequences that minimize the effects of both T_1 and T_2 weighting. Including a negative vascular contrast material (coated magnetite) into the imaging protocol allows the measurement EVLW [19] (studies on rats only).

Repeated measures of lung water by NMR vary by about 5–10% [20]. Numerous studies have reported a good correlation between NMR-determined estimates of lung water and estimates from the gold-standard gravimetric method [21–26]. A problem intrinsic to NMR imaging is that normal or mildly edematous lung produces relatively little signal using conventional spin-echo sequences on 1.5 Tesla imagers typically used for clinical purposes [18,25]. As a result, NMR methods can underestimate true lung water in absolute terms by as much as 20–40% [20,27,28] (despite the good correlation with gravimetric methods). This loss of signal is due to artifacts caused by the distinct and separate magnetic susceptibilities of both air and soft-tissue in the normally inflated lung. These artifacts, and therefore the loss of signal, are magnified by the strength of the external magnetic field. Recently, an imager that has only one-tenth the strength of most clinical scanners has been used along with a multi-echo pulse sequence (i.e. a 90° radiofrequency pulse followed by multiple 180° pulses) to minimize the effect of the air–soft-tissue artifact, resulting in an excellent correlation, even in absolute terms, between NMR and gravimetrically determined lung water [29]. This same NMR imaging sequence has also been successfully applied to normal volunteers [29].

T_1 and T_2 vary according to the type of tissue being examined, raising the theoretical possibility that NMR imaging could be used to identify differences in the composition of pulmonary edema generated by high intravascular pressures (low protein) as opposed to increased vascular permeability (high protein), potentially allowing the edema of heart failure to be distinguished non-invasively from the edema of acute respiratory distress syndrome (ARDS). These distinctions have been made (in rats) with the use of a 40 000 Dalton contrast material [30].

Cutillo *et al.* [31] have actually reported a method of NMR image analysis that takes advantage of the same signal loss artifact (the one caused by the air–soft-tissue interface) that confounds the measurement of proton density in absolute terms (and therefore of lung water) in the normally inflated lung. Since the air–soft-tissue interface is minimized as alveolar edema develops, the expected loss of signal is reduced. This difference in signal loss can be measured, leading to inferences about the location of the developing edema (alveolar edema causing less loss of signal than interstitial edema). To date, however, the method has only been applied to studies in rats [31].

In summary, the technique of NMR imaging continues to be developed as a quantitative tool to measure and monitor the development of pulmonary edema. An important advantage of using NMR to evaluate lung water is that the measurements can be obtained without any need for ionizing radiation. It is expensive, however, and even once the technical hurdles including respiratory and cardiac motion are overcome, considerable difficulty will undoubtedly be encountered when trying to implement such methods in the critically ill patient.

Positron emission tomography

Lung water can be measured by external residue detection techniques, after separately administering radioactively labeled tracers that distribute within the total and intravascular water spaces of the lung. Emissions are then detected with a device such as a gamma camera or a PET scanner. PET is widely held to be the gold standard for measuring EVLW (amongst the nuclear medicine techniques) because a tomographic image can then be created and normalized for the attenuation of the structure being imaged using a transmission (sometimes referred to as an attenuation) scan [32].

Lung water content can be measured either directly, or estimated from tissue density measurements [32,33]. With this approach, the water fraction of lung tissue must be assumed (0.82–0.84 ml/g). A small (~2%) correction for differences in tissue versus blood density can also be incorporated [34].

When lung water (instead of lung density) is measured directly, a sample of sterile water is labeled with a positron-emitting isotope, such as oxygen-15 ($H_2{}^{15}O$) (half-life = 2.06 min), and then administered intravenously. The O-15 labeled water is allowed to equilibrate within tissue water over a 3–4 min period (this makes inaccuracies from areas of hypoperfusion less significant), and the isotope's activity

concentration in lung tissue is then determined. If the activity data in the PET image are scaled to simultaneously obtained activity in the blood, the image can be displayed as a quantitative regional map of lung water distribution [35].

An analogous approach is used to measure the blood volume concentration in the images. In this case, O-15 (or, alternatively, C-11) labeled carbon monoxide is used instead of O-15 water. If O-15 carbon monoxide is used, trace amounts of $C^{15}O$ are inhaled as a gas, binding immediately to blood hemoglobin. After a few minutes, to allow equilibration within the body's blood volume, another PET scan is obtained. When again normalized to activity measurements in blood and corrected for attenuation, the image is a regional display of blood volume. An alternative to using peripheral blood samples is to measure the activity within the blood pool of a cardiac chamber. In this case, a further correction is necessary for the so-called 'partial volume averaging effect' (~5–10% in humans), which occurs as a result of the limited spatial resolution of PET relative to the size of the ventricular chamber [34]. With the assumption that 84% of blood is water (a reasonable assumption at normal hematocrits), the blood water content in a lung region can be subtracted from the total lung water concentration, yielding a derived image of extravascular water concentration [36]. The total time required to measure EVLW with PET is about 45 min, but repeat measurements can begin in as little as 10–15 min from the previous one.

Two previous studies showed that EVLW measurements by PET correlated well with EVLW measurements obtained by gravimetrics ($r = 0.86$–0.93), even though corrections for potential differences in peripheral versus capillary hematocrit, or for differences in tissue versus blood density were not included [36,37]. Perhaps because such corrections were not incorporated, PET estimates of EVLW systematically underestimated the gravimetric estimates by about 10–15%. PET measurements, however, are highly reproducible (coefficient of variation for repeat measurements $< 5\%$) and linear ($r = 0.99$ for changes in lung water over a 20-fold concentration range) [37]. The method also shows exquisite sensitivity: as little as 1 ml additional extravascular water can be detected with PET [37].

Despite these impressive performance characteristics, PET imaging is expensive (like NMR) and not widely distributed among medical centers (unlike NMR). Positron-emitting isotopes also produce ionizing radiation (although the amounts used in any one study are quite low). As with X-ray CT or NMR imaging, the patient must be taken to the PET facility for study, an obvious problem in critically ill patients.

Electrical impedance tomography (EIT)

Air and liquid offer different resistances to the flow of electricity through the body. Measuring thoracic bioelectrical impedance in response to a low amplitude alternating electric current passed through the body yields a value for resistivity which can be correlated to gravimetric EVLW after correction for weight [38–40]. Recent refinement using 'dynamic' cross-sectional reconstruction of this information 'gated' to the cardiac cycle (a source of electricity) may make this portable test more sensitive and specific [41] and, eventually, clinically attractive.

Indicator dilution methods

EVLW measurements can be obtained by indicator dilution methods using either the so-called 'mean transit time' or 'slope–volume' approaches to analyze the temperature–time or concentration–time data [42–45].

With the indicator dilution method, a freely diffusible (heat/cold) and a non-diffusible (indocyanine green dye which binds to albumin) indicator each have the same flow but through different volumes of distribution. The difference in the mean transit times of the two indicators is therefore extravascular thermal volume (ETV). In the slope–volume method, a slope for the linear decay of the thermodilution curve is determined by mixing within the largest volume through which the thermal indicator passes (lungs). When multiplied by the cardiac output, pulmonary thermal volume (PTV) can be calculated. Further correction for intrathoracic blood volume yields a value for EVLW. This can be achieved through injection of a single thermal indicator, obviating the need to use indocyanine green dye [46,47].

Since the extravascular water content of myocardium and non-pulmonary blood vessels is small relative to the extravascular water content of the lung, ETV and EVLW are usually considered to be equivalent. Many studies have shown that ETV usually (but not always) closely approximates EVLW [43,44]. The thermal capacitance of the non-aqueous structures may, however, be significant, leading to overestimates of EVLW of 10–15% [48]. Effros [42] and Allison *et al.* [44] have both pointed out that the measurement of ETV is only equal to EVLW if the relative transit times of the thermal indicator through red cells versus plasma, the relative specific heats of extravascular tissue versus plasma, the density of blood, and the fraction of extravascular mass represented by water are all taken into account. Without such corrections, ETV should consistently overestimate EVLW by as much as 24% in normal lungs. Interestingly, as the lungs become more edematous, a greater fraction of the extravascular mass becomes water, and the error introduced by ignoring these factors (which is the case with commercially available devices) actually goes down.

While the theory underlying these measurements is well understood [42], commercially available equipment may have seriously biased the interpretation of performance in

experimental and clinical settings [45,49,50]. In the only systems (COLD Z-03® and PiCCO®, Pulsion Medizintechnik, Munich, Germany) currently available for clinical use, many of the technical problems associated with the earlier equipment have apparently been addressed [44–46].

Overall, the correlation coefficient (r) for ETV and gravimetrically determined EVLW is usually at least 0.9 and the slope of the regression relationship is usually between 0.9 and 1.10 [43–45]. Using animal data, sensitivity has been estimated to be 88% and specificity 97%, with a coefficient of variation for repeated measurements of 4–8% [44]. This performance record in animals may be somewhat optimistic for the usual intensive care unit clinical setting. Using the 'COLD®' system, Zeravik *et al.* [51] reported a coefficient of variation of about 8%. Similarly, a strong correlation ($r = 0.98$) with close absolute agreement between ETV and gravimetric measurements obtained from the lungs of organ donors has been reported [48].

The advantages of measuring EVLW by the single or double indicator dilution methods are several; the methods are (superficially) simple to implement, safe, reproducible, and repeatable. On the other hand, they are somewhat invasive (it requires central venous as well as arterial catheterization). In addition, the accumulation of extravascular water in any portion of lung that is downstream from a large vascular obstruction cannot be detected [44]. An analogous problem exists for lung regions that are simply poorly perfused, for instance as a result of using positive end-expiratory pressure (PEEP) [42,44,52].

Conclusion

None of the methods for measuring EVLW, other than chest radiography, have been widely incorporated into clinical practice. One reason is undoubtedly that no one has shown that a measurement of EVLW *per se* is needed for sound clinical decision making during the treatment of pulmonary edema. Similarly, no one has shown that incorporating such methods into routine clinical practice will affect patient outcome. Although the potential value of having a quantitative measure of pulmonary edema seems obvious (such as a treatment endpoint surrogate for mortality in clinical trials) and various studies have suggested how such measurements might be used in clinical decision making [48], a convincing outcome study demonstrating benefit is still needed.

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