Research

Extravascular lung water assessed by transpulmonary single thermodilution and postmortem gravimetry in sheep
Mikhail Y Kirov¹, Vsevolod V Kuzkov¹, Vladimir N Kuklin¹, Kristine Waerhaug¹ and Lars J Bjertnaes²

¹Research Fellow, Department of Anesthesiology, Faculty of Medicine, University of Tromsø, Tromsø, Norway
²Professor, Chairman of the Department of Anesthesiology, Faculty of Medicine, University of Tromsø, Tromsø, Norway

Abstract

Introduction Acute lung injury is associated with accumulation of extravascular lung water (EVLW). The aim of the present study was to compare two methods for quantification of EVLW: transpulmonary single thermodilution (EVLWST) and postmortem gravimetric (EVLWG).

Methods Eighteen instrumented and awake sheep were randomly assigned to one of three groups. All groups received Ringer’s lactate (5 ml/kg per hour intravenously). To induce lung injury of different severities, sheep received Escherichia coli lipopolysaccharide 15 ng/kg per min intravenously for 6 hours (n = 7) or oleic acid 0.06 ml/kg intravenously over 30 min (n = 7). A third group (n = 4) was subjected to sham operation. Haemodynamic variables, including EVLWST, were measured using a PiCCOplus monitor (Pulsion Medical Systems, Munich, Germany), and the last measurement of EVLWST was compared with EVLWG.

Results At the end of experiment, values for EVLWST (mean ± standard error) were 8.9 ± 0.6, 11.8 ± 1.0 and 18.2 ± 0.9 ml/kg in the sham-operated, lipopolysaccharide and oleic acid groups, respectively (P < 0.05). The corresponding values for EVLWG were 6.2 ± 0.3, 7.1 ± 0.6 and 11.8 ± 0.7 ml/kg (P < 0.05). Ranges of EVLWST and EVLWG values were 7.5–21.0 and 4.9–14.5 ml/kg. Regression analysis between in vivo EVLWST and postmortem EVLWG yielded the following relation: EVLWST = 1.30 × EVLWG + 2.32 (n = 18, r = 0.85, P < 0.0001). The mean bias ± 2 standard deviations between EVLWST and EVLWG was 4.9 ± 5.1 ml/kg (P < 0.001).

Conclusion In sheep, EVLW determined using transpulmonary single thermodilution correlates closely with gravimetric measurements over a wide range of changes. However, transpulmonary single thermodilution overestimates EVLW as compared with postmortem gravimetry.

Keywords: acute lung injury, extravascular lung water, lipopolysaccharide, oleic acid, sheep

Introduction

Acute lung injury (ALI) of septic and non-septic origin is a frequent cause of mortality in critically ill patients. During ALI, the inflammatory process in the lungs may increase the microvascular pressure and permeability, resulting in an accumulation of extravascular lung water (EVLW) and development of pulmonary oedema [1]. However, it is difficult to estimate the amount of oedema fluid at the bedside. Clinical examination,
chest radiography and blood gases have proven to be of limited value in quantifying pulmonary oedema [1-3]. Several techniques to assess EVLW have therefore been developed.

Among the various methods for measurement of EVLW, thermo-dye dilution has been used most frequently [4-8]. In animal models of lung oedema, this method has been evaluated by comparison with postmortem gravimetry, which is supposed to be the ‘gold standard’ of EVLW measurements [7-9]. In critically ill patients, fluid management guided by thermo-dye measured EVLW was associated with improved clinical outcome [10]. Hence, EVLW has been suggested to play a role as an independent predictor of the prognosis and course of illness [6,8,10]. However, the thermo-dye dilution method is relatively time consuming, cumbersome and expensive. For these reasons, the method has not gained general acceptance [4,5,7].

Use of a technique based on injection of a single thermo-indicator that can be detected using an indwelling arterial catheter was an appealing concept. Recent experimental and clinical studies have shown that EVLW assessed by single thermodilution (ST) exhibits good reproducibility and close agreement with the thermo-dye double indicator technique [11,12]. The ST method is simpler to apply, less invasive and more cost effective; all of these factors make it more suitable for use at the bedside. However, to date, this new method has been sparsely evaluated against gravimetry [13,14], and further validation is needed.

Thus, the aim of the present study was to evaluate the accuracy of the ST technique by comparing it with that of postmortem gravimetry (EVLWGR) in conscious sheep, in which ALI was induced either by lipopolysaccharide (LPS) or by oleic acid (OA). Both of these models of ALI are reproducible and have been extensively described [7,9,11,15,16].

Methods

Surgical preparation and measurements

The study was approved by the Norwegian Experimental Animal Board and conducted in compliance with the European Convention on Animal Care. Eighteen yearling sheep weighing 27.5 ± 0.4 kg were instrumented, as a modification to previously described techniques [16-19], by inserting introducers into the left external jugular vein and common carotid artery. After 1–4 days of recovery, sheep were placed in an experimental pen. A thermodilution catheter (131HF7; Edwards Life Sciences, Irvine, CA, USA) was introduced into the pulmonary artery and a 4-Fr thermistor-tipped catheter (PV2014L16; Pulsion Medical Systems, Munich, Germany) into the carotid artery. The catheters were connected to pressure transducers (Transpac®III [Abbott, North Chicago, IL, USA] and PV8115 [Pulsion Medical Systems], respectively).

Mean pulmonary arterial pressure (PAP), pulmonary arterial occlusion pressure (PAOP) and right atrial pressure (RAP) were displayed on a 565A Patient Data Monitor (Kone, Espoo, Finland) and recorded on a Gould Polygraph (Gould Instruments, Cleveland, OH, USA). Heart rate, mean systemic arterial pressure, cardiac index (CI), systemic vascular resistance index, extravascular lung water index (EVLWI) assessed using the single thermodilution technique (EVLWIST), pulmonary vascular permeability index (PVPI), global end-diastolic volume (GEDV) index (GEDVI), intrathoracic blood volume (ITBV) index (ITBVI) and blood temperature were determined at 1-hour intervals using a PiCCOplus monitor (Pulsion Medical Systems). Every value reported here is the mean of three consecutive measurements, each consisting of a 10 ml bolus of ice-cold 5% dextrose injected into the right atrium randomly during the respiratory cycle.

To estimate EVLW we used the following formula [12]:

\[
\text{EVLW}_{\text{ST}} (ml) = \text{ITTV} \times \text{ITBV} \quad \text{(where ITTV is the intrathoracic thermal volume).}
\]

During clinical application of ST by means of the PiCCO monitor, ITBV is calculated as 1.25 × GEDV, the coefficient 1.25 being derived from critically ill patients [12]. However, in our previous investigations in sheep [17-19], in which ITBV was measured directly using the thermal-dye dilution technique, we found the coefficient to be 1.34 [14]. Thus, in the present study we used the corrected values of ITBVI, EVLWIST and PVPI, based on the following equation: ITBVI = 1.34 × GEDVI.

Blood samples were drawn from the systemic arterial (a) and pulmonary arterial (v) lines and analyzed every two hours for blood gases and haemoglobin (Rapid 860; Chiron Diagnostics Corporation, East Walpole, MA, USA). The pulmonary vascular resistance index (PVRI), venous admixture (Qs/Qt), oxygen delivery index (DO2I) and oxygen consumption index were calculated as described previously [16,19,20].

Experimental protocol

After establishing a stable baseline at time 0 hours, awake and spontaneously breathing sheep were randomly assigned to three experimental groups: a sham operated group (n = 4); a LPS group (n = 7), receiving an intravenous infusion of Escherichia coli O26:B6 LPS (Sigma Chemical, St. Louis, MO, USA) at 15 ng/kg per min for 6 hours; and an OA group (n = 7), in which sheep were subjected to an intravenous infusion of OA (Sigma Chemical) 0.06 ml/kg mixed with the animal’s blood. The duration of the infusion of OA was 30 min.

During the experiment, all animals received a continuous infusion (5 ml/kg per hour) of Ringer's lactate, aiming to maintain intravascular volume at baseline levels. After the last measurements, at 2 hours in the OA group and at 6 hours in the sham-operated and the LPS groups, the sheep were anaesthetized and killed with a lethal dose of potassium chloride. Then, post-
mortem EVLWI (EVLWG) was determined by gravimetry, as previously described [21-24].

**Statistical analysis**

For each continuous variable, normality was checked using the Kholmogorov-Smirnov test. Data are expressed as mean ± standard error of the mean, and assessed by analysis of variance followed by Scheffe’s test or test of contrasts, when appropriate. To evaluate the relationship between EVLWIST and EVLWIG, we used linear regression and Bland-Altman analysis. P < 0.05 was considered statistically significant.

**Results**

All animals survived until the end of the experiments. At baseline no significant differences were found between groups, as shown in Figs 1 and 2, and Tables 1 and 2. In the sham-operated sheep, all variables remained unchanged throughout the study.

**Haemodynamic and extravascular lung water measurements**

Figure 1 and Table 1 show that LPS and OA induced marked increments in PAP and PVRI, peaking at 1 hour and subsequently decreasing gradually to values significantly above the respective baselines and the corresponding values in the sham-operated group. PAOP and RAP also rose in both the LPS and the OA groups (P < 0.05; data not shown). In parallel, LPS increased EVLWIST transiently by 20–35% (P < 0.05; Fig. 1). After OA administration, EVLWIST rose to a maximum of 84% above baseline (P < 0.01). At the end of the experiment, EVLWIST in the OA group had increased by 6.4 ml/kg and 9.3 ml/kg relative to the LPS and the sham-operated groups, corresponding to increments of 54% and 104%, respectively (P < 0.05). PVPI increased by 40% after LPS administration and by 90% after OA (P < 0.05; Fig. 1). GEDVI and ITBVI varied within 10–15% of baseline with no intergroup differences. As shown in Table 1, LPS caused tachycardia and a rise in CI accompanied by a slight increase in mean arterial pressure whereas systemic vascular resistance index decreased (P < 0.05). In contrast, in the OA group CI declined and systemic vascular resistance index increased relative to baseline (P < 0.05).

**Oxygenation and gas exchange**

LPS caused significant increments in mixed venous oxygen saturation, DO2I and Qs/Qt (Fig. 2). OA decreased both arterial and venous oxygenation and reduced DO2I (P < 0.05). Oxygen consumption index did not change significantly (not shown). LPS caused a transient reduction in arterial carbon dioxide tension and a rise in pH (P < 0.05; Table 2). After OA, pH decreased (P = 0.04). The haemoglobin concentration as well as the body temperature rose only in the LPS group (P < 0.05).

**Linear regression and Bland-Altman analysis**

As shown in Fig. 3, the regression analysis between EVLWIST and postmortem EVLWIG yielded the following relation: EVLWIST = 1.30 × EVLWIG + 2.32 (n = 18, r = 0.85, P < 0.0001). Notably, the mean EVLWIST at the end of experiment was higher than EVLWIG: 13.6 ± 1.1 ml/kg versus 8.7 ± 0.7 ml/kg (P = 0.0005). Ranges of EVLWIST and EVLWIG values were 7.5–21.0 ml/kg and 4.9–14.5 ml/kg. According to the Bland-Altman analysis, the mean difference between EVLWIST and EVLWIG was 4.91 ml/kg, with upper and lower limits of agree-
ment (± 2 standard deviations) of +9.99 ml/kg and -0.17 ml/kg, respectively (Fig. 4). The difference between methods increased with increasing values of mean EVLWI (n = 18, r = 0.64; P = 0.005); the regression line equation was as follows: EVLWIST - EVLWIG = 0.89 × ([EVLWIST + EVLWIG]/2) + 6.82.

Postmortem gravimetry
As shown in Fig. 5, EVLWIG in the OA group increased by 4.7 ml/kg and 5.6 ml/kg relative to the LPS and the sham-operated groups, amounting to increments by 65% and 90%, respectively (P = 0.001).

Discussion
The present findings confirm that, in sheep, EVLW measured using the single transpulmonary thermodilution technique correlates closely with EVLW determined using postmortem gravimetry. However, EVLWIST overestimates EVLWIG, with the degree of overestimation increasing with the severity of ALI.

A number of experimental and clinical studies focused on the potential role of EVLW as a guide to diagnosis and treatment of critically ill patients [3,6-14,25,26]. During pulmonary oedema, accumulation of EVLW occurs before any changes take place in blood gases, chest radiogram and, ultimately, pressure variables. In addition, the latter variables are nonspecific diagnostic tools that are influenced by a variety of factors [2,4,5,8]. Thus, Boussat and coworkers [3] recently demonstrated that, in sepsis induced ALI, commonly used filling pressures such as PAOP and RAP are poor indicators of pulmonary oedema. Rather than those measures, they recommended direct measurement of EVLW. Consistent with this, we found that EVLW, in contrast to RAP, correlates with markers of lung injury in human septic shock [26]. Victims of

Table 1
Haemodynamics during acute lung injury in sheep

| Parameter | Group | Time point (hours) |
|-----------|-------|-------------------|
|           |       | 0     | 1     | 2     | 3     | 4     | 5     | 6     |
| PVRI (dyne·s/cm² per m²) | Sham | 117 ± 14 | 131 ± 19 | 141 ± 10 | 145 ± 11 | 114 ± 21 | 133 ± 13 | 151 ± 16 |
|          | LPS  | 115 ± 6  | 284 ± 20t | 240 ± 21t | 198 ± 31t | 193 ± 26t | 199 ± 23t | 182 ± 16t |
|          | OA   | 103 ± 9  | 351 ± 64f | 300 ± 45f | -       | -       | -       | -       |
| GEDVI (ml/m²) | Sham | 570 ± 46 | 601 ± 68 | 572 ± 43 | 566 ± 12 | 661 ± 74 | 607 ± 67 | 655 ± 60 |
|          | LPS  | 571 ± 23 | 620 ± 57 | 564 ± 32 | 579 ± 42 | 598 ± 38 | 624 ± 42 | 615 ± 37 |
|          | OA   | 646 ± 38 | 629 ± 60 | 590 ± 55 | -       | -       | -       | -       |
| ITBVI (ml/m²) | Sham | 764 ± 62 | 806 ± 91 | 766 ± 58 | 759 ± 16 | 886 ± 99 | 813 ± 90 | 878 ± 81 |
|          | LPS  | 785 ± 30 | 831 ± 76 | 756 ± 43 | 776 ± 57 | 801 ± 51 | 836 ± 57 | 825 ± 49 |
|          | OA   | 866 ± 51 | 912 ± 42 | 790 ± 74 | -       | -       | -       | -       |
| HR (beats/min) | Sham | 106 ± 6  | 104 ± 8  | 96 ± 7  | 91 ± 5  | 99 ± 6  | 98 ± 11 | 97 ± 5  |
|          | LPS  | 96 ± 4   | 122 ± 6t | 109 ± 6 | 109 ± 4t | 109 ± 8 | 122 ± 4t | 130 ± 5t |
|          | OA   | 111 ± 5  | 104 ± 13 | 102 ± 13 | -       | -       | -       | -       |
| CI (l/min per m²) | Sham | 5.7 ± 0.3 | 5.5 ± 0.3 | 5.2 ± 0.3 | 5.1 ± 0.2 | 5.4 ± 0.4 | 5.2 ± 0.3 | 5.3 ± 0.3 |
|          | LPS  | 5.7 ± 0.1 | 7.3 ± 0.5tt | 5.9 ± 0.2 | 5.8 ± 0.3 | 5.6 ± 0.4 | 6.2 ± 0.3t | 6.8 ± 0.2tt |
|          | OA   | 6.1 ± 0.3 | 4.5 ± 0.3f | 4.6 ± 0.5 | -       | -       | -       | -       |
| MAP (mmHg) | Sham | 102 ± 5  | 101 ± 6  | 101 ± 6 | 101 ± 5 | 102 ± 5 | 102 ± 5 | 101 ± 4  |
|          | LPS  | 94 ± 4   | 104 ± 5t | 105 ± 3t | 106 ± 4t | 105 ± 3t | 104 ± 5t | 100 ± 6  |
|          | OA   | 94 ± 4   | 101 ± 2  | 104 ± 4f | -       | -       | -       | -       |
| SVRI (dyne·s/cm² per m²) | Sham | 1453 ± 101 | 1496 ± 125 | 1589 ± 138 | 1536 ± 105 | 1579 ± 109 | 1607 ± 119 | 1681 ± 169 |
|          | LPS  | 1410 ± 81 | 1128 ± 102f | 1352 ± 62 | 1515 ± 107 | 1428 ± 101 | 1308 ± 79 | 1126 ± 58t |
|          | OA   | 1266 ± 63 | 1847 ± 368 | 1670 ± 147f | -       | -       | -       | -       |

Data are expressed as mean ± standard error of the mean. *P < 0.05, LPS versus sham-operated group; †P < 0.05, versus t = 0 hours in LPS group; ‡P < 0.05, OA versus sham-operated group; §P < 0.05, versus t = 0 hours in OA group; llP < 0.05, LPS versus OA group. CI, cardiac index; GEDVI, global end-diastolic volume index; HR, heart rate; ITBVI, intrathoracic blood volume index; LPS, lipopoly saccharide; MAP, mean arterial pressure; OA, oleic acid; PVRI, pulmonary vascular resistance index; Sham, sham-operated; SVRI, systemic vascular resistance index.
ALI, regardless of pathogenesis, have a significantly higher EVLW than do other patients [6,26]. Hence, measurement of EVLW supports the diagnosis and may even improve clinical outcomes when used cautiously in combination with treatment protocols that are known to hasten the resolution of pulmonary oedema [10,25].

Instrumented awake sheep represents a stable experimental model for measuring cardiopulmonary variables, as demonstrated in the sham-operated group in the present study as well as by other investigators [15,27]. The model can be used to assess different interventions during ALI.

Consistent with previous investigators [15,17,27], we observed that infusion of LPS and OA caused pulmonary hypertension, increased EVLW and impaired gas exchange. Despite increments in PAP, PAOP and PVRI, both ITBV and GEDV remained constant whereas PVPI (an index of microvascular permeability, calculated as the ratio of EVLW to pulmonary blood volume) increased significantly. Thus, the haemodynamic responses to LPS and OA are not purely hydrostatic but may also manifest as noncardiogenic permeability pulmonary oedema [13,15-18,27,28].

In the present study lung oedema was significantly more severe in the OA group than in the LPS group, which is consistent with the findings of other investigators [29]. In fact, OA causes acute haemorrhagic alveolitis, which may lead to acute endothelial and alveolar necrosis and a severe proteinaceous oedema [30]. In contrast, the LPS-induced ALI is initiated by accumulation of granulocytes and lymphocytes in the pulmonary microcirculation that results in more moderate damage to endothelial cells and lung oedema [31].

Lung injury in the LPS group was accompanied by a hyperdynamic circulatory state, which was manifested by systemic vasodilation and increments in CI and DO2I toward the end of the experiment. In contrast, in the OA group we observed cardiac depression and systemic vasoconstriction. This is consistent with previous investigations of LPS and OA [18,27,30,32]. Thus, ovine models exhibit a scatter of cardiopulmonary changes from normal in the sham-operated group to mild or moderate ALI in endotoxaemic sheep and moderate to severe ALI in animals subjected to OA.

The significant correlation of EVLW_{ST} and EVLW_{IG} observed in the present study is consistent with findings of Katzenelson and coworkers [13], who validated EVLW_{ST} versus postmortem gravimetry in dogs [13]. However, those investigators did not specifically assess the relationship between EVLW_{ST} and EVLW_{IG} in sepsis-induced ALI. In addition, their study was performed in anaesthetized and mechanically ventilated animals; hence, further investigation of the correlation in a conscious state was required. Recently, ST has been evaluated against the thermo-dye dilution method in both experimental and clinical settings [11,12]. The studies revealed a close agreement between the techniques. Thus, we believe that injection of cold saline can provide valuable information about the EVLW content and the severity of pulmonary oedema.

During ALI, both ST and postmortem gravimetry demonstrated similar relative increases in EVLW as compared with sham-operated animals. However, we noticed that ST overestimates the absolute values of EVLW compared with the gravimetric
**Table 2**

Gas exchange during acute lung injury in sheep

| Parameter          | Group | 0          | 2          | 4          | 6          |
|--------------------|-------|------------|------------|------------|------------|
|                    |       | 0246       | 0246       | 0246       | 0246       |
| pHa                | Sham  | 7.52 ± 0.03 | 7.53 ± 0.02 | 7.50 ± 0.02 | 7.50 ± 0.02 |
|                   | LPS    | 7.48 ± 0.01 | 7.50 ± 0.02 | 7.55 ± 0.02* | 7.53 ± 0.02 |
|                   | OA     | 7.50 ± 0.01 | 7.44 ± 0.03† | -          | -          |
| PaCO₂ (mmHg)       | Sham  | 38.7 ± 2.7  | 36.4 ± 2.1  | 36.4 ± 1.6  | 37.4 ± 1.0  |
|                   | LPS    | 39.7 ± 1.4  | 38.8 ± 1.5  | 32.6 ± 0.6‡ | 33.1 ± 1.0  |
|                   | OA     | 36.4 ± 1.1  | 42.5 ± 3.7  | -          | -          |
| Haemoglobin (g/dl) | Sham  | 10.7 ± 0.9  | 10.1 ± 0.6  | 10.2 ± 0.5  | 10.3 ± 0.5  |
|                   | LPS    | 10.4 ± 0.6  | 10.4 ± 0.6  | 11.0 ± 0.7* | 10.9 ± 0.6  |
|                   | OA     | 10.3 ± 0.4  | 10.7 ± 0.5  | -          | -          |
| Blood temperature (°C) | Sham  | 39.3 ± 0.1  | 39.2 ± 0.1  | 39.3 ± 0.1  | 39.3 ± 0.1  |
|                   | LPS    | 39.3 ± 0.1  | 40.0 ± 0.1* | 41.3 ± 0.1* | 41.0 ± 0.1* |
|                   | OA     | 39.5 ± 0.1  | 39.6 ± 0.1  | -          | -          |

Data are expressed as means ± standard error of the mean. *P < 0.05, versus t = 0 hours in LPS group; †P < 0.05, OA versus sham operated group; ‡P < 0.05, LPS versus sham-operated group. LPS, lipopolysaccharide; OA, oleic acid; PaCO₂, arterial carbon dioxide tension; Sham, sham-operated.

**Figure 3**

Linear regression analysis between extravascular lung water index (EVLWI) as determined by transpulmonary single thermodilution (EVLWiston) and postmortem gravimetry (EVLWigravimetry) in sheep. EVLWiston = 1.30 × EVLWigravimetry + 2.32 (n = 18, r = 0.85, P < 0.0001). Line of identity is dashed; 95% confidence intervals are indicated by solid lines. LPS, lipopolysaccharide; OA, oleic acid; Sham, sham-operated.

**Figure 4**

Bland-Altman plot for the extravascular lung water index (EVLWI) measured using transpulmonary single thermodilution (EVLWiston) and postmortem gravimetry (EVLWigravimetry) in sheep. The x-axis shows the mean of EVLWI measurements by single thermodilution and gravimetry. The y-axis shows the difference between the methods. The bold line indicates the value for the mean difference between EVLWiston and EVLWigravimetry (bias), and each dashed line indicates two standard deviations (SDs). Mean difference EVLWiston - EVLWigravimetry = 4.91 ml/kg (SD 2.54 ml/kg).
technique – a discrepancy that increased with progression of pulmonary oedema. This finding could be accounted for by heat exchange of the thermal indicator with extravascular intrathoracic structures, such as the walls of the large vessels and the myocardium, and by recirculation of the indicator [8]. In addition, the coefficients for calculation of EVLWIST and ITBV may vary with weight and age, as well as between animal species [11]. Consequently, in the experimental setting EVLWIST requires a specific correction. In the present study we replaced the coefficient 1.25 used in humans in the ITBVI equation (i.e. ITBVI = 1.25 × GEDVI) with the recalculated ‘ovine’ coefficient 1.34 [14], which is based on 426 measurements in 48 animals [17-19].

In contrast to ST, the thermo-dye dilution technique runs the risk of underestimating EVLW in comparison with gravimetry [4]. This underestimation increases during ALI caused by instillation of hydrochloric acid into the airways, and has been explained by redistribution of pulmonary blood flow away from the oedematous areas. The redistribution is thought to prevent indicator diffusion and consequently to prevent detection of oedema [7]. In addition, detection of EVLW by thermo-dye dilution can be impaired by changes in CI as well as by positive end-expiratory pressure during mechanical ventilation [8,28].

Compared with other techniques for assessment of EVLW, ST may underestimate EVLW during pulmonary oedema due to intratracheal instillation of saline, although it is an accurate method in normal lungs [33]. However, intratracheal instillation of saline can also be criticized because a proportion of the fluid is rapidly absorbed and obscured from detection [34].

Notably, the use of postmortem gravimetry as the reference method for evaluating pulmonary oedema also has limitations [21,33]. For example, the method only allows one measurement and is therefore of no use in following variations over time. The application of gravimetry is limited almost exclusively to experimental studies. The comparison of gravimetric measurement with results of other techniques for determination of EVLW can be influenced by the duration from death to removal of the lungs and by pathophysiological changes in the lungs after cardiac arrest. Thus, the gravimetric technique can underestimate the real value of EVLWI because of partial reabsorption of fluid before excision of the lungs.

**Conclusion**

The determination of EVLW by ST in sheep correlates closely with gravimetric measurements over a wide range of changes, and thus it may potentially be of benefit in quantifying lung oedema in critically ill patients. However, compared with post-mortem gravimetry, single transpulmonary thermodilution overestimates the absolute values of EVLW. Thus, further studies are warranted to evaluate the accuracy of this method for managing ALI in humans.

**Key messages**

- In sheep, extravascular lung water assessed by transpulmonary single thermodilution correlates closely with gravimetric measurements over a wide range of changes.
- Despite a moderate overestimation of the extravascular lung water content compared with post-mortem gravimetry, single thermodilution can be a useful tool for assessment of pulmonary oedema during ALI.

**Competing interests**

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**Author contributions**

MYK participated in the design of study, performed statistical analysis, and drafted the manuscript. VKK participated in the design of study, performed statistical analysis, and prepared the figures. VKK and KW participated in the design of study. LJB participated in the design of study and provided coordination. All authors read and approved the final manuscript.

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References

1. Martin GS, Bernard GR: Airway and lung in sepsis. Intensive Care Med 2001, 27(Suppl 1):S63-S79.
2. Halperin BD, Feeley TW, Mhm FG, Chiles C, Guthaner DF, Blank NE: Evaluation of the portable chest roentgenogram for quantitating extravascular lung water in critically ill adults. Chest 1985, 88:649-652.
3. Bousa S, Jacques T, Ley B, Laurent E, Gache A, Capellier G, Richthardt A: Intravascular volume monitoring and extravascular lung water in septic patients with pulmonary edema. Intensive Care Med 2002, 28:712-718.
4. Pfeiffer UJ, Backus G, Blumel G, Eckart J, Muller P, Winkler P, Rossi P, Oldner A, Wanecek M, Leksell LG, Rudehill A, Konrad D, Martin GS, Bernard GR: Critical Care 2003, 7:122.
5. Sakka SG, Ruhl CC, Pfeiffer UJ, Beale R, McLuckie A, Reinhart K, Bock J, Lewis FR: Critical Care Med 1992, 20:129-139.
6. Boldt J: Clinical review: hemodynamic monitoring in the intensive care unit. Crit Care 2002, 6:52-59.
7. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A: Prognostic value of extravascular lung water in critically ill patients. Chest 2002, 122:2080-2086.
8. Roch A, Michael P, Lambert D, Dellaux S, Saby C, Perrin G, Ghez O, Bregen F, Thomas P, Carpentier JP, 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 2004, 32(9):11-118.
9. Bock J, Lewis FR: Clinical relevance of lung water measure-ment with the thermal-dye dilution technique. In Practical Applications of Fiberoptics in Critical Care Monitoring. Edited by: Lewis FR, Pfeiffer UJ. Berlin, Heidelberg, New York: Springer; 1990:114-121.
10. Neumann P: Extravascular lung water correlates with acute lung injury and outcome in human septic shock [abstract]. Acta Anaesth Scand 2003, 47:31.
11. Nakazawa H, Noda H, Noshima S, Flynn J, Traber LD, Herndon DN, Traber DL: Pulmonary transvascular fluid flux and cardiovascular function in sheep with chronic sepsis. J Appl Physiol 1993, 75:2521-2528.
12. Groeneveld ABJ, Verheij J: Is pulmonary edema associated with a high extravascular thermal volume? Crit Care Med 2004, 32:999-101.
13. Neumann P, Berglund JE, Mondejar EF, Magnusson A, Hedenstierna G: Dynamics of lung collapse and recruitment during pro-longed breathing in porcine lung injury. J Appl Physiol 1998, 95:353-134.
14. Schuster DP: ARDS: clinical lessons from the oleic acid model of acute lung injury. Am Rev Respir Crit Care Med 1994, 149:249-260.
15. Brigham KL, Meynick B: Endotoxin and lung injury. Am Rev Respir Dis 1986, 133:913-927.
16. Stubbe HD, Westphal M, Van Aken H, Hucklebruch C, Lauer S, Jahn UR, Hinder: F: Inhaled nitric oxide reduces lung edema during fluid resuscitation in ovine acute lung injury. Intensive Care Med 2003, 29:1790-1797.
17. Fernandez-Mondejar E, Castano-Perez J, Rivera-Fernandez R, Colmenero-Ruiz M, Manzano F, Perez-Villares J, de la Chica R: Quantification of lung water by transpulmonary thermocdiolation in normal and edematous lung. J Crit Care 2003, 18:253-258.
18. Cheesunet MS, Nuckton TJ, Golden J, Folkesson HG, Matthay MA: Rapid alveolar epithelial fluid clearance following lung lavage in pulmonary alveolar proteinosis. Chest 2001, 120:271-274.

Critical Care December 2004 Vol 8 No 6 Kirov et al.