Accuracy and Limits of Transpulmonary Dilution Methods in Estimating Extravascular Lung Water After Pneumonectomy

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Study objectives: The measurement of extravascular lung water index by double indicator (EVLWIDI) or the measurement of extravascular lung water index by transpulmonary thermodilution (EVLWITT) could be useful after pneumonectomy. Since pulmonary blood flow and volume are altered after pneumonectomy, the validity of these methods is uncertain. This study has compared measurements of EVLWIDI and EVLWITT with measurement of extravascular lung water index by gravimetry (EVLWIG) in a porcine model of pulmonary edema induced after right pneumonectomy.

Design: Randomized laboratory study.

Setting: Animal research laboratory.

Subjects: Twenty-seven female pigs; mean weight, 35 ± 5 kg (± SD).

Interventions: The pigs were anesthetized, placed on mechanical ventilation, and allocated to a two-lung group (n = 10) or a right pneumonectomy group (n = 17). EVLWIDI and EVLWITT were measured at baseline, 60 min after pneumonectomy, and 60 min after IV injection of oleic acid (OA).

Measurements and results: There was a good correlation between EVLWIG and EVLWIDI values (r = 0.96, p < 0.0001 in the two-lung group; and r = 0.81, p = 0.02 in the pneumonectomy group). EVLWIDI underestimated EVLWIG in the two-lung group (~3 mL/kg; 95% confidence interval [CI], −7 to +2 mL/kg) and in the pneumonectomy group (~0.9 mL/kg; 95% CI, −3.3 to +1.5 mL/kg). After pneumonectomy, EVLWITT decreased in mean by 27% and increased in mean by 70% after OA acid. There was a good correlation between EVLWIG and EVLWITT values (r = 0.96, p < 0.0001 in the two-lung group; and r = 0.90, p < 0.0001 after pneumonectomy). EVLWITT slightly overestimated gravimetric value in the two-lung group (+1.5 mL/kg; 95% CI, −1.5 to +4.2 mL/kg) and largely overestimated gravimetric value after pneumonectomy (+5 mL/kg; 95% CI, +3.4 to +6.8 mL/kg).

Conclusion: Double-indicator and transpulmonary thermodilution methods could be useful in monitoring extravascular lung water index (EVLW) after pneumonectomy, but transpulmonary thermodilution largely overestimates EVLWI.

Key words: double indicator; extravascular lung water; gravimetry; pig; pneumonectomy; transpulmonary thermodilution

Abbreviations: CI = confidence interval; EVLW = extravascular lung water index; EVLWIDI = extravascular lung water index by double indicator; EVLWITT = extravascular lung water index by transpulmonary thermodilution; EVLWIG = measurement of extravascular lung water index by gravimetry; FIO2 = fraction of inspired oxygen; GEDVI = global end-diastolic volume index; ICG = indocyanine green; ITBVI = intrathoracic blood volume index; MPAP = mean pulmonary artery pressure; OA = oleic acid; PPE = postpneumonectomy pulmonary edema

Pneumonectomy is a major surgery with a high postoperative mortality rate, mainly due to pulmonary complications. Beside bacterial pneumonia and bronchopleural fistula, postpneumonectomy pulmonary edema (PPE) occurs in 2 to 4%, and its incidence has not shown any noticeable decrease in the last decades. Since mortality in patients with PPE can reach 75 to 100%, early diagnosis by quantification of extravascular lung water may be useful for early therapeutic approach. Chest radiography is the most commonly used diagnostic tool for PPE, but its low diagnostic accuracy makes it unsuitable for adequate and early management of PPE, notably because of hyperin-
lation of the remaining lung. The double-indicator method allows quantitative assessment at the bedside of cardiac output and extravascular lung water index (EVLWI) by body weight with good accuracy and reproducibility.\(^8,9\) This method uses temperature and indocyanine green (ICG) dye dilution to derive intrathoracic thermal volume index and intrathoracic blood volume index (ITBVI) in order to estimate EVLWI (EVLWI = intrathoracic thermal volume index – ITBVI). Single-indicator thermal dilution, a less expensive and less time-consuming method, has been validated against gravimetric and double-indicator methods.\(^10,11\) Single-indicator thermal dilution estimates ITBVI based on the usually linear relationship between global end-diastolic volume index (GEDVI) and ITBVI demonstrated in previous studies.\(^10,12\) Since GEDVI is derived from the characteristics of the thermodilution curve, the need for ICG dilution is eliminated.

One should ask, however, if these methods are valid in patients with one lung. First, pneumonectomy may induce a variable fall in pulmonary blood volume. Therefore, the relation between ITBVI and GEDVI may not be linear. Second, following pneumonectomy, an increase in blood flow to a restricted capillary volume could induce a reduction in the mean transit time of the thermal indicator, resulting in a failure of heat to equilibrate between intravascular and extravascular compartments and to a misestimation of intrathoracic thermal volume. It is unknown if those factors only induce a limited bias in the determination of ITBVI and EVLWI by transpulmonary thermodilution, or if the correlation between thermal dilution and reference gravimetric values is affected. Therefore, the aim of this study was to evaluate the accuracy of double-indicator and thermodilution methods in a one-lung porcine model of pulmonary edema.

Materials and Methods

The study protocol was approved by the local veterinary ethics committee. Twenty-seven, 4-month old, female pigs (mean weight, 35 ± 5 kg [± SD]) were studied.

Anesthesia and Mechanical Ventilation

After premedication by the IM injection of midazolam, 2 mg/kg, anesthesia was induced and maintained by the IV infusion of midazolam and fentanyl. Saline solution (7 mL/kg/h) was infused continuously throughout anesthesia. Animals were tracheotomized and mechanical ventilation was administered via cannula (inner diameter, 8 mm; Mallinckrodt Medical; Hazelwood, MO), with a tidal volume of 10 mL/kg, a constant fraction of inspired oxygen (FiO\(_2\)) of 0.8, and an inspiration/expiration ratio of 1:2 without positive end-expiratory pressure (Servo 900C; Siemens; Elema, Sweden). The respiratory rate was adjusted to obtain arterial P\(_{\text{CO}_2}\) from 35 to 45 mm Hg.

Experimental Protocol

Animals were randomly allocated to a two-lung group or a pneumonectomy group. In the two-lung group, five animals served as control animals and five animals received IV oleic acid (OA). 0.1 mL/kg, in the superior vena cava through the proximal port of the pulmonary artery catheter.

In the pneumonectomy group, 4 animals served as control animals and 13 animals received OA (0.75 mL to 2.5 mL randomly assigned per animal in order to obtain variable amounts of pulmonary edema). Measurements were performed in double-lung ventilation, after 60 min of stabilization after pneumonectomy, and 60 min after IV injection of OA.

One-Lung Ventilation and Right Pneumonectomy

Tracheostomy cannula was removed, and a single-lumen reinforced tracheal tube with cuff (inner diameter, 7.0 mm; Rüsch; Gauting, Germany) was advanced through the tracheostomy orifice in the left mainstem bronchus using a fiberoptic bronchoscopy. One-lung ventilation of the left lung was initiated with a tidal volume of 7 mL/kg, a constant FiO\(_2\) of 0.8, and an inspiration/expiration ratio of 1:2 without positive end-expiratory pressure. The respiratory rate was adjusted to obtain arterial P\(_{\text{CO}_2}\) not exceeding 55 mm Hg in one-lung ventilation. The animal was positioned on the left side, and a right thoracotomy was performed. Attention was paid to avoid blood loss. Placing a chest retractor between fourth and fifth ribs exposed the right lung. After dissection of the hilum, the pulmonary arteries, veins, and bronchus were ligated and the lung was resected. The chest was closed, and the animal was replaced in the supine position. Ventilatory settings were kept constant throughout the study period.

Monitoring

A 5F catheter was inserted in the left carotid artery for monitoring of systemic pressures and arterial blood gases. A pulmonary artery catheter (Baxter Healthcare Corporation; Irvine, CA) was inserted via the right external jugular vein in the left pulmonary artery under fluoroscopic control. Systemic and pulmonary arterial pressures were measured at end-expiration. Cardiac index was measured by injection of three 12-mL boluses of 5% glucose solution between 0° and 5°C via a closed system at end-inspiration. Study data correspond to the mean of three measurements.
\( \text{PaO}_2 \) and \( \text{PaCO}_2 \) were measured by a blood gas analyzer (278-Blood Gas System; Ciba Corning; Medfield, MA). The pulmonary vascular resistance index and intrapulmonary shunt or venous admixture were calculated using standard formulas. Body surface area was calculated using the following formula: body surface area = \( \frac{K \times \text{weight}}{1000^2} \), where \( K = 0.112 \) for pigs.

**Statistical Analysis**

The water content of blood, homogenate, 5,000 revolutions per minute at 5°C for 30 min to obtain water. Aliquots of the whole homogenate were centrifuged at blended to a homogenized state with an equal amount of distilled cardiogenic edema. Then, left lung was removed, weighed, and hemoglobin concentration. As soon as possible after killing the animal using an overdose of thiopental, exsanguination and and EVLWI were expressed as mean ± SD. The distribution of data was checked. Results are expressed as mean ± SD. A repeated-measures analysis of variance was used to analyze the evolution of parameters after pneumonectomy. The Student Newman-Keuls test was used for comparisons between times when analysis of variance showed a statistical significance. The correlation between EVLWITt, EVLWI, and EVLWIG values was performed using Pearson product correlation. Bias with 95% confidence intervals (CIs) was determined using the method of Bland and Altman. For all tests, \( p \leq 0.05 \) was considered statistically significant.

**RESULTS**

**Evolution of Respiratory and Hemodynamic Parameters After Pneumonectomy and OA Injection**

In the two-lung group, OA induced a decrease in \( \text{PaO}_2/\text{FiO}_2 \) (97 ± 40 mm Hg vs 458 ± 52 mm Hg in control animals) and cardiac index (3.2 ± 0.4 L/min/m\(^2\) vs 4.7 ± 0.8 L/min/m\(^2\)) and an increase in shunting (38 ± 12% vs 13 ± 5%) and mean pulmonary artery pressure (MPAP) [34 ± 5 mm Hg vs 15 ± 2 mm Hg].

Right pneumonectomy resulted in a decrease in \( \text{PaO}_2/\text{FiO}_2 \) ratio (Table 1), accompanied by an increase in shunting. It induced a significant increase in MPAP accompanied by a limited decrease in cardiac index. OA injected after pneumonectomy produced an additional decrease in \( \text{PaO}_2/\text{FiO}_2 \) ratio, an additional increase in MPAP, and a decrease in cardiac index. There was a good correlation between cardiac index measured by the pulmonary artery catheter and transpulmonary thermodilution (\( r = 0.95, p < 0.0001 \)).

**EVLWIG**

In the two-lung group, EVLWIG was 6.4 ± 1 mL/kg in animals not receiving OA and 14.5 ± 3 mL/kg in animals receiving OA (Fig 1). In the pneumonectomy group, EVLWIG was 3.6 ± 0.5 in animals not receiving OA and 5.8 ± 1 mL/kg in animals receiving OA (Fig 1).

**Correlation Between Gravimetric and Double-Indicator Methods**

There was a good correlation between EVLWIG and EVLWITt values (\( r = 0.96, p < 0.00001 \) in two-lung animals; and \( r = 0.81, p = 0.02 \) after pneumonectomy), but EVLWITt underestimated gravimetric value by 20 to 30% (Fig 1). Bias for the EVLWITt – EVLWIG measurement was −3 mL/kg (95% CI, −7 to +2 mL/kg) in two-lung animals and −0.9 mL/kg (95% CI, −3.3 to +1.5 mL/kg) after pneumonectomy.

**Correlation Between Gravimetric and Transpulmonary Thermodilution Methods**

**Two-Lung Group:** There was a good correlation between EVLWIG and EVLWITt values provided by the PiCCO System (\( r = 0.96, p < 0.00001 \)).
values provided by the COLD-System were also well correlated to gravimetric values ($r = 0.91$, $p < 0.0001$). EVLWITTT by the PiCCO System slightly overestimated gravimetric value, whereas EVLWITTT by the COLD-System slightly underestimated it. Indeed, bias for the EVLWITTT – EVLWIG measurement by the PiCCO System was +1.5 mL/kg (95% CI, −1.5 to +4.25 mL/kg) and by the COLD System was −1 mL/kg (95% CI, −4 to +3 mL/kg) [Fig 2, 3].

**Pneumonectomy Group:** After pneumonectomy, EVLWITTT decreased in mean by 27% and increased in mean by 70% after OA injection (Table 1). There was a good correlation between EVLWIG and

<table>
<thead>
<tr>
<th>Variables</th>
<th>Before Pneumonectomy</th>
<th>After Pneumonectomy</th>
<th>After OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PaO}_2/\text{FiO}_2$, mm Hg</td>
<td>490 ± 95</td>
<td>267 ± 138†</td>
<td>169 ± 62†</td>
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<td>Intrapulmonary shunt, %</td>
<td>3.5 ± 5</td>
<td>23 ± 10†</td>
<td>33 ± 10‡</td>
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<tr>
<td>$\text{PaCO}_2$, mm Hg</td>
<td>42 ± 6</td>
<td>53 ± 6‡</td>
<td>62 ± 9‡</td>
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<td>Peak airway pressure, cm H$_2$O</td>
<td>14 ± 2</td>
<td>28 ± 3†</td>
<td>33 ± 5†</td>
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<td>Mean arterial pressure, mm H$_2$O</td>
<td>106 ± 12</td>
<td>113 ± 4</td>
<td>104 ± 3</td>
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<tr>
<td>MPAP, mm Hg</td>
<td>17 ± 3</td>
<td>28 ± 6†</td>
<td>34 ± 6†</td>
</tr>
<tr>
<td>PVRI, dyne · s · cm$^{-1}$ · m$^2$</td>
<td>197 ± 56</td>
<td>450 ± 150‡</td>
<td>579 ± 268‡</td>
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<tr>
<td>Cardiac index by PAC, L/min/m$^2$</td>
<td>5.4 ± 1</td>
<td>4.8 ± 0.8</td>
<td>4.2 ± 0.5</td>
</tr>
<tr>
<td>CI by double indicator$_i$</td>
<td>5.5 ± 1</td>
<td>5.0 ± 1.6</td>
<td>4.3 ± 0.7</td>
</tr>
<tr>
<td>CI by transpulmonary thermodilution (PiCCO System)</td>
<td>5.6 ± 1</td>
<td>5.1 ± 1.6</td>
<td>4.4 ± 0.7</td>
</tr>
</tbody>
</table>

**EVLWIDI**
- Without OA ($n = 4$) 3.7 ± 1.5 1.8 ± 0.7† 2.4 ± 0.6‡
- With OA ($n = 13$) 3.5 ± 0.9 2.1 ± 0.8‡ 4.7 ± 1.5‡

**EVLWITTT by PiCCO System**
- Without OA ($n = 4$) 9.1 ± 1.6 7 ± 1.6 7.8 ± 0.9
- With OA ($n = 13$) 8.2 ± 1 6 ± 1.4 10.3 ± 1.1‡

**ITBVI by double indicator**
- Without OA ($n = 4$) 732 ± 131 640 ± 143† 690 ± 153
- With OA ($n = 13$) 534 ± 106 584 ± 219 598 ± 204

*Data are presented as Mean ± SD. PVRI = pulmonary vascular resistance index; PAC = pulmonary artery catheter.

†$p < 0.01$ vs before pneumonectomy, Student Newman Keuls test.
‡$p < 0.05$ vs after pneumonectomy, Student Newman Keuls test.

**Figure 1.** EVLWIG, EVLWIDI, and EVLWITTT (mean ± SD).
EVLWTT values ($r = 0.90$, $p < 0.0001$ for the PiCCO System [Fig 2]; and $r = 0.95$, $p < 0.0001$ for the COLD-System). However, the two devices (mainly the PiCCO System) overestimated EVLWIT T. Indeed, bias for the EVLWIT T - EVLWIG measurement by the PiCCO System was +5 mL/kg (95% CI, +3.4 to +6.8 mL/kg) [Fig 3], whereas for the COLD-System it was +2 mL/kg (95% CI, +2 to +6 mL/kg). As shown on the Bland-Altman plot (Fig 3), the overestimation of EVLWIT T provided by the PiCCO System tended to increase with the amount of EVLWI.

Influence of Right Pneumonectomy on ITBVI

Measures of ITBVIDI decreased by 10% after pneumonectomy (Table 1). As already described,10 there was a linear relationship between ITBVI and GEDVI measured by the double-indicator method before pneumonectomy. Indeed, regression analysis in the 17 animals of the pneumonectomy group revealed ITBVI of 1.42 and GEDVI of +49 mL (p < 0.001). After pneumonectomy, there was a less reliable linear relationship (ITBVI of 1.29 and GEDVI of +53 mL; p = 0.03). This result showed that calculation of ITBVI based on PiCCO System settings could lead to an overestimation of ITBVI by approximately 10% after pneumonectomy as compared with values before resection.

Discussion

The results of the present study showed that the EVLWI amount measured by double-indicator and transpulmonary thermodilution methods were correlated to the gravimetric measurement after pneumonectomy. Therefore, these methods could be useful to follow the evolution of EVLWI amount after pneumonectomy. However, absolute values of EVLWI were overestimated by the transpulmonary thermodilution after pneumonectomy. This overestimation is quite important, since it could lead to double the true values of EVLWI when pulmonary edema is moderate. Since we found normal gravimetric values after pneumonectomy to be approximately 3.6 mL/kg, values >5 mL/kg should be considered to be high. Since bias of thermal dilution is approximately +5 mL/kg after pneumonectomy, EVLWIT T should be interpreted cautiously, notably when it is from 5 to 8 mL/kg, i.e., the range of values in which EVLWI could be considered elevated whereas in fact it is not. Concerning the double-indicator method, it underestimated EVLWI by 20 to 30% and was not biased after pneumonectomy.

It is difficult to reproduce experimentally PPE because of its complex pathophysiology. Indeed, involved mechanisms may be ischemia-reperfusion injury,16 capillary stretching resulting from an increased pulmonary capillary pressure,16 and volutrauma because of overinflation of the remaining lung.17,18 To our knowl-
edge, the distribution of injury at the early stage of PPE has not been studied. However, early PPE could have some characteristics of an indirect diffuse lung injury. It is the first reason why we chose OA injury to mimic PPE. The second reason is the well-known accuracy of double-indicator and transpulmonary thermal dilution methods in this model.9,11,19

Our findings of an underestimation of EVLWI by the double-indicator method and of a slight overestimation of EVLWI by transpulmonary thermodilution in animals with both lungs is in agreement with previous reports.9,11,19,20 The underestimation of EVLWI by the double-indicator method could be explained in part by the ventral redistribution of pulmonary blood flow. Indeed, IV OA is known to produce a relatively diffuse edema as shown by thin-section CT scan, more particularly in the few hours after injury;21 but a moderate redistribution of blood flow occurs toward the spared ventral regions.22 This redistribution could prevent indicator diffusion leading to an underestimation of intrathoracic thermal volume. The overestimation by the thermodilution method could be explained first, by a thermal equilibration with myocardium and vessel walls leading to an increase in thermal volume, and second, by the fact that the PiCCO System uses coefficients for calculation of ITBVI with GEDVI that are appropriate for human use. By measuring ITBVI by the double-indicator method, we found that the relationship between GEDVI and ITBVI was different in pigs as compared with the correlation showed in humans, leading to an underestimation of ITBVI by the PiCCO System in pigs and to an overestimation of EVLWI. However, it does not explain why the overestimation of EVLWI by the PiCCO System monitor increases after pneumonectomy. Indeed, since ITBVI is calculated with the same equation after pneumonectomy, underestimation of ITBVI by the PiCCO System is less than in two-lung animals. It should lead to a decrease in overestimation of EVLWI. Overestimation after pneumonectomy could be partly due to the variability of the relationship between GEDVI and ITBVI that is higher than in two-lung animals. Moreover, technical characteristics of the device (catheter thermistor, software) could be involved. Indeed, COLD-System provided GEDVI values that were lower than with the PiCCO System and overestimated EVLWI less than the PiCCO System.

Limitations of the Study

First, we measured EVLWI 1 h after induction of edema. Therefore, we cannot assume that EVLWI measured by thermodilution methods are still well correlated with gravimetry several hours or days after lung injury. Second, we induced a moderate increase in EVLWI with OA after pneumonectomy because animals could not have survived to a greater edema. Therefore, we do not know the accuracy of transpulmonary thermodilution and double-indicator methods if EVLWI amount is very high after pneumonectomy. From our results, it is likely that the greater the edema the greater the overestimation by transpulmonary thermodilution. This increasing overestimation would however have limited consequences on the diagnostic accuracy of the thermal dilution method since it could not lead to an erroneous diagnostic of PPE, real values being elevated.

Clinical Implications for the Management of PPE

The main interest of EVLWI measurement could be in early diagnosing and monitoring PPE. Clinical signs of PPE such as dyspnea, hypoxemia, and markedly reduced lung compliance are usually delayed between 1 day and 3 days after surgery and are moreover unspecific of PPE.3,4 At an early stage, edema is mainly interstitial and badly detected by chest radiography because of the overinflation of the remaining lung. Early EVLWI measurement may therefore be useful in identifying patients at risk for
respiratory failure. However, since our laboratory study only evaluated correlation between gravimetric and thermodilution values, the ability of thermodilution methods in predicting occurrence of PPE should be confirmed in the clinical setting in order to assess its usefulness. Indeed, whether the early detection of an increase in EVLWI will permit patients to be identified who will progress to manifest PPE and whether such an early detection could impact management and outcome of patients presenting with PPE remains to be evaluated.

In patients with PPE, the loss of the alveolar endothelial integrity could be, in part, due to stretching of the capillaries by increased pulmonary vascular resistances, or occur through shear stresses acting on the endothelium due to the hyperdynamic pulmonary circulation caused by resection of lung tissue. In this way, the monitoring of cardiac output after pneumonectomy could be useful to evaluate the relation between cardiac output and occurrence of PPE. From our experience, the use of a pulmonary artery catheter after pneumonectomy is not recommended because of pulmonary arterial sutures. Since we found a very good correlation between cardiac output measurements by pulmonary artery catheter and thermodilution, this method could represent an alternative to monitoring cardiac output securely after pneumonectomy. Consequently, simultaneous monitoring of cardiac output, EVLWI, and ITBVI could help to further understand whether increase in pulmonary blood flow or increase in vascular permeability is the main determinant of PPE. It could therefore help in determining which preventive treatments could be efficient.

In summary, our results showed that EVLWI measured by double-indicator and transpulmonary thermodilution methods is well correlated to gravimetric measurement in pigs submitted to a right pneumonectomy. Double-indicator measurement of EVLWI is not biased by pneumonectomy. Concerning transpulmonary thermodilution, it constantly and significantly overestimates EVLWI after pneumonectomy but accurately detects a moderate increase in EVLWI, as produced in this study. It could therefore be useful in diagnosing PPE and monitoring EVLWI amount after pneumonectomy. In order to further improve the estimation of EVLWI by thermal dilution, the correlation equation between ITBVI and GEDVI after right or left pneumonectomy should be defined in human.

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