Factors influencing the estimation of extravascular lung water by transpulmonary thermodilution in critically ill patients*

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Objective: **To investigate factors that may influence the estimation of extravascular lung water (EVLW) with a single (cold) indicator compared with assessment using two indicators (thermo-dye dilution).**

Design: Post hoc **analysis of an electronic hemodynamic database.**

Setting: **Surgical intensive care unit of a university hospital.**

Patients: **Forty-eight critically ill patients monitored by the thermo-dye dilution technique in the postoperative period.**

Interventions: **None.**

Measurements and Main Results: **The EVLW was simultaneously assessed by the thermo-dye dilution technique ($EVLW_{ref}$) and estimated by transpulmonary thermodilution ($EVLW_{est}$). $EVLW_{ref}$ index ranged between 1 and 40 mL/kg (mean 10 ± 7 mL/kg) and $EVLW_{est}$ between 2 and 39 mL/kg (mean 9 ± 6 mL/kg). $EVLW_{ref}$ was closely correlated (r = .96) with $EVLW_{est}$. The mean difference (bias) between $EVLW_{ref}$ and $EVLW_{est}$ was −0.5 ± 1.9 mL/kg. The bias was not influenced by the weight, height, body surface area, body mass index, Pao_2, intrathoracic blood volume, cardiac output, or dosage of vasoactive agents. In contrast, the bias was slightly but significantly influenced by $EVLW_{ref}$, Pao_2/Fio_2 ratio, tidal volume, and level of positive end-expiratory pressure.**

Conclusions: **In our surgical intensive care unit population, the estimation of EVLW by transpulmonary thermodilution was influenced by the amount of EVLW, the Pao_2/Fio_2 ratio, the tidal volume, and the level of positive end-expiratory pressure. However, compared with the double indicator method, transpulmonary thermodilution estimation remained clinically acceptable even in patients with severe lung disease. (Crit Care Med 2005; 33:1243–1247)**

KEY WORDS: extravascular lung water; pulmonary edema; extravascular thermal volume; transpulmonary thermodilution; indocyanine green; critically ill patients

Transpulmonary thermodilution has been shown to be a reliable technique for assessing cardiac output (1) and cardiac preload (2) and is being used increasingly for hemodynamic monitoring in critically ill patients. This technique has also been proposed to estimate extravascular lung water (EVLW), and hence, to quantify pulmonary edema (3). The estimation of EVLW by the injection of a single thermal (cold) indicator is based on the assumption that the ratio between the maximum volume of blood contained in the heart and in the pulmonary circulation remains consistently equal to 4:1 (3). This method has been shown to compare favorably with the double-indicator (thermo-dye) dilution technique (3) and more recently with the *ex vivo* gravimetric method (4).

However, several anatomical (weight, height), mechanical (tidal volume, positive end-expiratory pressure [PEEP]), physiologic (pulmonary edema, hypoxic pulmonary vasoconstriction), and pharmacologic (vasoactive agents) factors may affect the pulmonary blood volume (5–7) and/or heart dimensions (8). Whether these factors may also affect the heart/pulmonary blood volume ratio, and hence the estimation of EVLW by transpulmonary thermodilution, has not been investigated.

Therefore, the aim of the present study was to investigate in surgical intensive care unit (ICU) patients which factors may influence the accuracy of EVLW estimation by transpulmonary thermodilution compared with the double-indicator dilution assessment.

MATERIALS AND METHODS

Patients. We studied 48 mechanically ventilated patients (30 men, mean age = 65 ± 17 yrs) admitted to the surgical ICU of Rhenish Westfalian Technical University (Aachen, Germany) in the postoperative period of gastrointestinal (n = 16), colorectal (n = 14), esophageal (n = 7), pancreatic (n = 4), hepatic (n = 3), or coronary artery bypass graft (n = 1) surgery or for trauma (n = 3). All selected patients were monitored by the COLD System (Pulsion Medical Systems, Munich, Germany) according to the decision of the treating physician because of hemodynamic instability and/or severe hypoxemia related to sepsis (n = 29), hemorrhage (n = 3), or nosocomial pneumonia (n = 16). Cardiorespiratory variables were collected in an electronic database (Excel, Microsoft corporation, Redmond, WA) and are summarized in Table 1. The institutional review board of Rhenish Westfalian University waived the need for informed consent for the *post hoc* analysis of hemodynamic evaluations.

Double-Indicator Dilution Measurements: The Reference EVLW. All patients were instrumented with a 4-Fr thermistor-tipped, fiberoptic femoral arterial catheter (PV2024, Pulsion) connected to the COLD System (Z-021, software version 5.1) for the analysis of thermal and dye dilution curves. Measurements were made in triplicate by the central venous injection of a 15-mL, iced 5% dextrose solution with 2.5 mg/mL indocyanine green. After injection of the cold indocyanine green solution, the thermistor-tipped fiberoptic catheter recorded the dye dilution curve and the thermodi-

*See also p. 1428.

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Table 1. Cardiorespiratory characteristics of the study population

	Mean ± SD	Extreme Values
Hemodynamic variables		
Heart rate, beats/min	98 ± 23	42–170
Mean arterial pressure, torr	78 ± 15	37–121
Cardiac index, L/min/m^2	3.6 ± 0.9	1.9–7.1
ITBV index, mL/m^2	969 ± 210	564–1792
Respiratory variables		
$EVLW_{ref}$ index, mL/kg	10 ± 7	1–40
$EVLW_{est}$ index, mL/kg	9 ± 6	2–39
PaO_2, mm Hg	86 ± 22	46–239
PaO_2/FIO_2, mm Hg	201 ± 94	48–571
Tidal volume, mL/kg	11 ± 2	6–15
PEEP, cm H_2O	4 ± 3	0–14

ITBV, intrathoracic blood volume; $EVLW_{ref}$, reference extravascular lung water; $EVLW_{est}$, estimated extravascular lung water; PEEP, positive end-expiratory pressure.

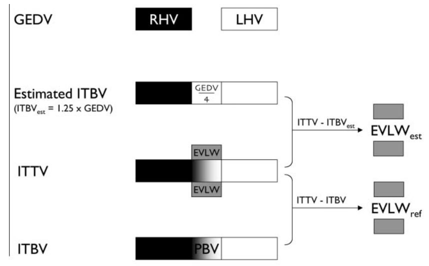

Figure 1. Extravascular lung water (*EVLW*) assessment by the double indicator (thermo-dye) dilution technique (*$EVLW_{ref}$*, reference EVLW) and estimation by transpulmonary thermodilution (*$EVLW_{est}$*, estimated EVLW). *GEDV*, global end-diastolic volume; *RHV*, right heart volume; *LHV*, left heart volume; *ITBV*, intrathoracic blood volume; *ITTV*, intrathoracic thermal volume; *PBV*, pulmonary blood volume.

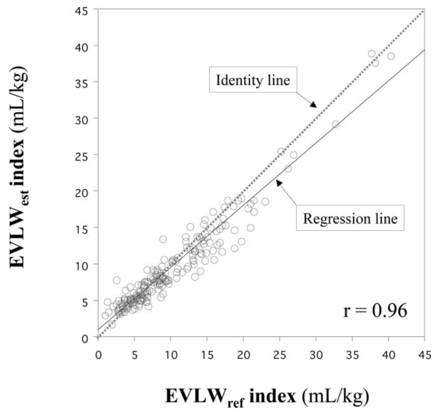

Figure 2. Relationship between extravascular lung water assessed by the double indicator dilution technique (*$EVLW_{ref}$*) and estimated by transpulmonary thermodilution (*$EVLW_{est}$*).

lution curve. The determination of flow and volume by this method is based on the simultaneous application of the two indicators: one that is diffusible into the extravascular pulmonary tissue compartment (temperature) and another that is nondiffusible (indocyanine green). Femoral artery cardiac output is determined by a standard thermodilution technique that has been previously validated against the pulmonary artery thermodilution and the Fick method (1, 9). The calculation of intracardiac and intrathoracic volumes is performed by an analysis of the transit times of the indicators derived from the dilution curves. By multiplying cardiac output with the mean transit time of each indicator, the volume between the sites of injection and indicator detection can be calculated (10). The intrathoracic blood volume (ITBV) calculation is based on the dye dilution curve, whereas the intrathoracic thermal volume (ITTV) calculation is based on the thermodilution curve. The difference between the volume of distribution of the thermal and the dye indicators (i.e., ITTV − ITBV) represents the EVLW ($EVLW_{ref}$) (Fig. 1).

Single-Indicator Dilution Measurements: The Estimated EVLW. Multiplying the cardiac output with the downslope time of the thermodilution curve results in the pulmonary thermal volume, which is the largest single mixing volume for the cold indicator (11). The difference between the ITTV (the volume of distribution of the cold indicator) and the pulmonary thermal volume gives the maximum volume of blood contained in the four heart chambers, called the global end-diastolic volume (GEDV). Assuming that the ratio between the GEDV and the pulmonary blood volume is equal to 4:1 (3), the ITBV can be estimated as follows:

$$\text{Estimated ITBV} = \text{pulmonary blood volume} + \text{GEDV} = 1.25 \times \text{GEDV} \quad [1]$$

The difference between the ITTV and the estimated ITBV gives an estimation of EVLW ($EVLW_{est}$) (Fig. 1).

Other Measurements and Calculations. During each hemodynamic evaluation, the following variables were also collected in the electronic database: weight, height, body surface area (Dubois formula), body mass index (weight/height^2), tidal volume, PEEP, PaO_2, FIO_2, and dosage of vasoactive agents (epinephrine, norepinephrine, dopamine, dobutamine).

Statistical Analysis. All selected patients had at least four hemodynamic evaluations during their stay in the surgical ICU. To consider the same number of measurements per patient, only the first four measurements were considered for statistical analysis. Linear regression analysis (using the Spearman rank method) and the Bland-Altman method were used to compare $ELWI_{est}$ and $ELWI_{ref}$ and to investigate which factors may influence the difference between $ELWI_{est}$ and $ELWI_{ref}$ (12). Results were expressed as mean ± SD. Differences between subgroups of patients were compared using a Mann-Whitney test. We considered $p < .05$ as statistically significant.

RESULTS

One hundred ninety-two (4 × 48) measurements were available for analysis.

$EWLW_{ref}$ index ranged from 1 to 40 mL/kg (mean 10 ± 7 mL/kg) and $EVLW_{est}$ index from to 2 to 39 mL/kg (mean 9 ± 6 mL/kg). $EVLW_{ref}$ index was closely correlated with $EVLW_{est}$ index (r = .96, Fig. 2). Over the study period, individual changes in $EVLW_{ref}$ ranged from −17 to 11 mL/kg and were closely correlated (r = .93) with changes in $EVLW_{est}$ index (Fig. 3).

The mean difference (bias) between $EVLW_{est}$ index and $EVLW_{ref}$ index was −0.5 ± 1.9 mL/kg (Fig. 4). The bias was not correlated with the weight (range, 45–116 kg); height (154–191 cm); body surface area (1.4–2.3 m^2); body mass index (18–37 kg/cm^2); PaO_2 (46–239 torr); dosage of epinephrine (0–20 μg/min), norepinephrine (0–25 μg/min), dopamine (0–1000 μg/min), or dobutamine (0–800 μg/min); ITBV index (564–1792 mL/m^2); or cardiac index (1.9–7.1 L/min/m^2).

In contrast, the bias was weakly but significantly correlated with the $EVLW_{ref}$ index (r = .51, $p < .0001$), tidal volume (r = .32, $p < .0001$), level of PEEP (r = .30, $p < .0001$), and PaO_2/FIO_2 ratio (r = −.23, $p < .01$). Biases ± SD in different subgroups of patients are presented and compared in table 2.

DISCUSSION

Pulmonary edema is defined as the abnormal accumulation of fluid in the extravascular space of the lung. An increase in EVLW is associated with disturbances of lung volume, lung mechanics, and gas exchange and always represents a potential threat to life. In 373 critically ill patients,

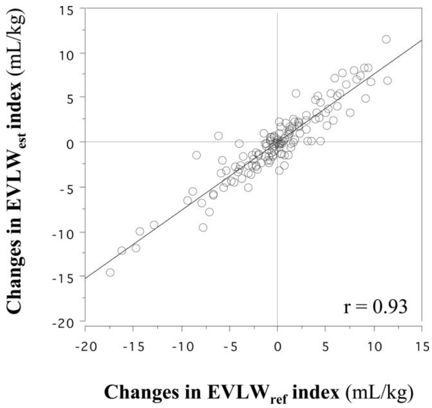

Figure 3. Relationship between changes in extravascular lung water assessed by the double indicator dilution technique (*EVLW$_{ref}$*) and estimated by transpulmonary thermodilution (*EVLW$_{est}$*).

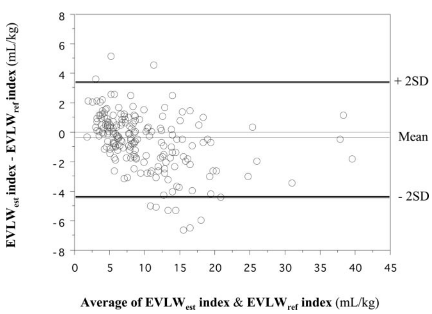

Figure 4. Bland-Altman representation of extravascular lung water assessed by the double indicator dilution technique (*EVLW$_{ref}$*) and estimated by transpulmonary thermodilution (*EVLW$_{est}$*). The bias increases with extravascular lung water.

Table 2. Extravascular lung water measured by the double indicator dilution technique (EVLW$_{ref}$) and bias between the double and the single indicator dilution techniques (EVLW$_{est}$ index minus EVLW$_{ref}$ index) in different subgroups of patients

All Measurements	No.	EVLW$_{ref}$ Index, mL/kg	Bias ± SD, mL/kg
	192	10 ± 7	−0.5 ± 1.9
EVLW$_{ref}$ index, mL/kg			
<7	82	5 ± 1	0.4 ± 1.2
≥7	110	14 ± 6	−1.3 ± 1.9[a]
Tidal volume, mL/kg			
<12	134	8 ± 5	−0.1 ± 1.6
≥12	58	15 ± 8	−1.5 ± 2.1[a]
PEEP, cm H_2O			
<5	119	9 ± 7	−0.1 ± 1.6
≥5	73	13 ± 6	−1.2 ± 2.0[a]
PaO_2/FIO_2, torr			
<200	113	13 ± 7	−0.9 ± 2.0
≥200	79	6 ± 3	0.1 ± 1.5[b]

PEEP, positive end-expiratory pressure.
[a] $p < .0001$ and [b] $p < .001$, comparison of bias between subgroups.

Sakka et al. (13) found that the mortality rate was approximately 65% in patients with an EVLW level >15 mL/kg, whereas the mortality rate was approximately 33% in patients with an EVLW level <10 mL/kg. Pulmonary edema is commonly detected on physical examination and confirmed through chest radiography by the presence of bilateral pulmonary opacities. However, chest radiography abnormalities, arterial hypoxemia, and reduced lung compliance are not specific to pulmonary edema and hence correlate only very weakly with the amount of EVLW (14). In this regard, the current international definition of acute lung injury/acute respiratory distress syndrome lacks accuracy in identifying patients with pulmonary edema (15). A quantitative assessment of pulmonary edema can be made at the bedside by the measurement of EVLW using dilution techniques. In patients with cardiac and noncardiac pulmonary edema, using EVLW instead of occlusion pressure to guide fluid therapy may significantly reduce positive fluid balance, duration of mechanical ventilation, and ICU length of stay (16). There was also some evidence that the EVLW-guided treatment reduced mortality rate in patients with permeability pulmonary edema (14). Therefore, the bedside assessment of EVLW may be very useful in identifying and quantifying pulmonary edema and hence in selecting patients who might benefit from a fluid restriction/depletion therapeutic strategy based on EVLW monitoring (14, 16).

Several techniques have been proposed to directly assess EVLW in humans (17). Among these techniques, the double indicator (thermo-dye) dilution has been used most frequently in ICU patients, since other techniques (computed tomography scan, magnetic resonance imaging, positron emission tomography) are not currently available at the bedside (17). The double indicator dilution technique is, however, relatively time consuming, cumbersome, and expensive and has not been widely incorporated into clinical practice. Transpulmonary thermodilution has been proposed as an alternative technique to estimate EVLW (3). The accuracy of EVLW estimation depends on two assumptions. The first assumption is that the downslope time of the thermodilution curve times the cardiac output truly gives the pulmonary thermal volume and hence allows an accurate estimation of GEDV (11). The second assumption is that the ratio between the GEDV and the pulmonary blood volume is consistently equal to 4:1. Although recently confirmed by Reuter et al. (18) in cardiac surgery patients, this ratio may not pertain to all patients and for a given patient to all clinical circumstances. Our study demonstrates that anatomical factors such as weight, height, body surface area, or body mass index do not significantly affect the estimation of EVLW by transpulmonary thermodilution. Physiologic factors like PaO_2, ITBV, and cardiac output have also no significant influence, at least for the range of values observed in our patients. Actually, this range was quite large, including severely hypoxemic patients ($46 \leq PaO_2 \leq 239$ torr), hypo- and hypervolemic patients ($564 \leq$ ITBV index ≤ 1791 mL/m^2, normal range 850–1000 mL/m^2) (3, 9, 18), and hypo- and hyperdynamic states ($1.9 \leq$ cardiac index ≤ 7.1 L/min/m^2). Similarly, the use of vasoactive or inotropic agents did not affect the difference between the estimated and reference EVLW.

In contrast, the amount of EVLW, the tidal volume, the PEEP level, and the PaO_2/FIO_2 ratio (an indicator of the severity of lung disease) (19) were found to affect the accuracy of EVLW estimation. Edematous lung areas may compress pulmonary vessels and enhance pulmonary vasoconstriction, both factors that may reduce pulmonary blood volume (5, 20, 21) and hence lead to overestimation of ITBV and underestimation of EVLW (EVLW is estimated as ITTV minus estimated ITBV). Our findings are consistent with a recent experimental study (22) suggesting that EVLW estimation by transpulmonary thermodilution may be less accurate in injured edematous lungs than in normal lungs. In this latter study, *The amount of extravascular lung water, the Pa_{O_2}/F_{IO_2} ratio, the tidal volume, and the level of positive end-expiratory pressure may slightly but significantly affect the estimation of extravascular lung water by transpulmonary thermodilution.*

EVLW was estimated before and after lung instillation of saline in animals with or without oleic acid lung injury. The volume of instilled saline was less accurately detected by transpulmonary thermodilution in injured than in normal lungs. However, these results have to be interpreted cautiously since the instilled saline may have been absorbed and hence cleared from the lungs more rapidly in injured than in normal lungs (23). The slight but significant underestimation of EVLW that we observed in our patients with pulmonary edema is also consistent with findings reported by Sakka et al. (3) in 209 critically ill patients. Indeed, although they did not specifically study factors affecting the estimation of EVLW by transpulmonary thermodilution, these authors noted that $EVLW_{est}$ slightly underestimated high $EVLW_{ref}$ values (3). In our study, the tidal volume and the PEEP level were also found to affect the accuracy of EVLW estimation. An increase in tidal volume or in PEEP may induce a decrease in pulmonary blood volume (5, 6) and changes in right and left ventricular dimensions (8), both factors that may also change the heart/pulmonary blood volume ratio.

Importantly, if our study demonstrates that the mean difference between $EVLW_{ref}$ and $EVLW_{est}$ increased with several factors, it also shows that the bias remained below 10% and hence can be considered as clinically acceptable even in the subgroups of patients with a Pa_{O_2}/F_{IO_2} ratio <200 torr or ventilated with a PEEP ≥5 cm H_2O (Table 2). However, our patients were ventilated with a relatively low level of PEEP (mean PEEP = 4 ± 3 cm H_2O). Therefore, whether transpulmonary thermodilution also accurately estimates EVLW in patients ventilated with higher levels of PEEP remains to be determined. In patients with pulmonary edema, defined by an $EVLW_{ref}$ index ≥7 mL/kg (17), transpulmonary thermodilution tends to underestimate (−9%) EVLW (Table 2, Figs. 2 and 4). But interestingly, based on our findings, a correction factor could be systematically applied to improve the accuracy of EVLW estimation. For example, adding 1 mL/kg to all $EVLW_{est}$ index values >7 mL/kg would result in a bias (± SD) of 0 ± 2 mL/kg in this subgroup of patients. If our findings were confirmed by other teams, this correction could be automatically done by transpulmonary thermodilution monitors. Finally, the higher bias (10%) was observed in patients ventilated with a tidal volume ≥12 mL/kg (Table 2), but such a ventilatory strategy has been shown to be harmful and is not recommended or used anymore in patients with acute lung injury (24).

Although the double indicator technique has been validated against the *ex vivo* gravimetric method (17), there has been concern that in the setting of acute lung injury the heterogeneity of lung perfusion makes the accuracy of the method less reliable (25). In this regard, it must be noted that the aim of the present study was not to validate the assessment of EVLW by transpulmonary thermodilution but to investigate factors that may affect the estimation of EVLW with a single indicator compared with the assessment using two indicators.

CONCLUSIONS

The amount of EVLW, the Pa_{O_2}/F_{IO_2} ratio, the tidal volume, and the level of PEEP may slightly but significantly affect the estimation of EVLW by transpulmonary thermodilution. However, compared with the double indicator dilution method, the transpulmonary thermodilution technique provides a clinically acceptable estimation of EVLW, even in patients with severe lung disease.

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