Accuracy of transpulmonary thermodilution versus gravimetric measurement of extravascular lung water

Rita Katzenelson; Azriel Perel; Haiim Berkenstadt; Sergei Preisman; Samuel Kogan; Leonid Sternik; Eran Segal

Objective: Pulmonary edema is a severe and often life-threatening condition. The diagnosis of pulmonary edema and its quantification have great clinical significance and yet can be difficult. A new technique based on thermodilution measurement using a single indicator has recently been developed (PiCCO, Pulsion Medical Systems, AG Germany). This method allows the measurement of extravascular lung water and thus can quantify degree of pulmonary edema. The technique has not been compared with a gold standard, gravimetric measurement of extravascular lung water. Therefore, the objective of this study was to determine the ability of extravascular lung water measurement with the PiCCO monitor (PiCCO, Pulsion Medical Systems AG, Munich, Germany) in a dog model of pulmonary edema. Design: Prospective, randomized animal study. Setting: A university animal research laboratory.

Subjects: Fifteen mongrel dogs (n = 5/group) weighing 20–30 kg. Interventions: The dogs were anesthetized and mechanically ventilated. Five dogs served as controls; in five dogs hydrostatic pulmonary edema was induced using inflation of a left atrial balloon combined with fluid administration to maintain a high pulmonary artery occlusion pressure; and in five dogs pulmonary edema was induced by intravenous injection of oleic acid. After a period of stabilization in a state of pulmonary edema, extravascular lung water was measured with the PiCCO monitor. The animals were then killed, and extravascular lung water was measured using a gravimetric technique.

Measurements and Main Results: There was a very close (r = .967, p < .001) relationship between transpulmonary thermodilution and gravimetric measurements. The measurement with the PiCCO was consistently higher, by 3.01 ± 1.34 mL/kg, than the gravimetric measurement.

Conclusions: Measurement of extravascular lung water using transpulmonary thermodilution with a single indicator is very closely correlated with gravimetric measurement of lung water in both increased permeability and hydrostatic pulmonary edema. (Crit Care Med 2004; 32:1550–1554)

Key Words: pulmonary edema; extravascular lung water; gravimetric technique

Pulmonary edema (PE) is a common finding in many critically ill patients. The pathophysiological mechanism leading to PE is accumulation of fluid in the interstitial and alveolar space in the lungs, termed extravascular lung water index (EVLWI). In PE, the patient’s outcome, ventilation days, and ICU length of stay are closely related to the level of extravascular lung water accumulation (1).

Therefore, a method for measurement of EVLWI at the bedside to enable direction of fluid management is of great importance. A number of methods are used to assess degree of EVLWI; among these are the chest radiograph, and pulmonary artery occlusion pressure (PAOP) measurement with a pulmonary artery catheter. However, these methods have been shown to be inaccurate and nonspecific (2–4).

Until recently, in vivo quantitative assessment of EVLWI could be performed only with a combined thermo-dye dilution technique (5). However, this technique is cumbersome and time consuming and has not gained widespread clinical use. A technique that enables measurement of EVLWI using a single-indicator thermodilution is incorporated into the PiCCO monitor (PiCCO, Pulsion Medical Systems AG, Munich, Germany), which is quite commonly used in Europe and Australia for hemodynamic monitoring. This technique only requires an injection of a bolus of cold injectate into a central vein and the detection of the thermodilution curve in a large artery. From this curve the EVLWI can be calculated. The technique is easily applied to the clinical setting and has been compared with double-indicator thermodilution in clinical series (6). It has not yet been validated against a gold standard of pulmonary edema measurement—the gravimetric technique of EVLWI measurement.

We therefore compared EVLWI measurements in a dog model of oleic acid-induced pulmonary edema and hydrostatic pulmonary edema by the single-indicator thermodilution with gravimetric method.

METHODS

The study was performed in accordance with the National Institutes of Health guidelines and after approval of the local animal care committee of the Sheba Medical Center. Anesthesia. After premedication with intramuscular ketamine 5 mg/kg and midazolam 0.2 mg/kg, anesthesia was induced by intravenous thiopentone 4mg/kg, fentanyl 0.002 mg/kg, and pancuronium bromide 0.1 mg/kg. The trachea was intubated and the
lungs were ventilated with a tidal volume of 10 mL/kg to achieve an end-tidal \( P_{\text{CO}} \), of 32–36 mm Hg. Anesthesia was maintained using inhaled isoflurane 1%. Body temperature was controlled at \( 38 \pm 0.5^\circ \text{C} \) with an external heat source. The dogs were placed supine throughout the experiment.

**Instrumentation.** A 4-Fr thermodilution catheter (PV2014L16, Pulsion Medical Systems AG) was placed via cutdown into the femoral artery. A 7.5-Fr triple-lumen flow-directed pulmonary artery catheter (VIP Swan-Ganz, Edwards Lifesciences, Irvine, CA) was inserted into the right or left internal jugular vein via cutdown.

**Monitoring.** Blood pressure, pulmonary artery pressure, and electrocardiogram were recorded continuously. Cardiac output was recorded at baseline and before killing the animals after stabilization.

**Determination of EVLWI by Thermodilution.** EVLWI was determined using a PiCCO Monitor (Pulsion Medical Systems AG). In the PiCCO method, a bolus of iced or room temperature saline is injected through the central venous catheter and the change in temperature is measured with a femoral artery thermistor-tipped catheter. The underlying principle of EVLW determination using a single indicator is based on the measurement of blood volume as determined from the thermodilution curve.

Analysis of thermodilution curve allows calculation of these important compartments: the volume of distribution of the indicator (cold) named intrathoracic thermal volume (ITTV), and the largest compartment that the indicator passes from the site of injection to the site of detection, which is termed pulmonary thermal volume (PTV). ITTV is measured directly and is the product of cardiac output and the mean transit time (Mtt). Mtt is the time at which 50% of the injected indicator is detected:

\[
\text{ITTV} = \text{CO-MTT} \quad [1]
\]

In 1951, Newman et al. (7) demonstrated that in a series of mixing chambers with identical flow, the decay of the dilutional curve is determined by the largest compartment. Thus, when cold saline is injected into a central vein and detected in the femoral artery, the largest mixing chamber that is the PTV can be determined from the product of the cardiac output and the exponential decay time (\( T_{\text{expdec}} \)) from the thermodilution curve:

\[
\text{PTV} = \text{CO-}T_{\text{expdec}} \quad [2]
\]

The ITTV consists of PTV and the global end-diastolic volume (GEDV), which is the maximal volume of all heart chambers. Therefore,

\[
\text{GEDV} = \text{ITTV} - \text{PTV} \quad [3]
\]

Intrathoracic blood volume (ITBV) is the blood volume of the heart chambers and the pulmonary blood volume. This volume is linearly related to GEDV and can be estimated from this value.

The linear relation between ITBV and GEDV was established in studies comparing EVLW measurement with double-indicator and single-indicator technique (6). The ITBV in this study was directly measured by thermo-dye dilution technique. In this method, the GEDV was measured using thermal indicator, and ITBV was measured using dye. The dye used, indocyanine green, is bound to plasma proteins and remains in the intravascular space, and its volume of distribution as the difference between ITBV and the site of detection equals ITBV. A linear relationship was found between the ITBV and the GEDV. The linear relation between ITBV measured by thermo-dye dilution technique and GEDV is expressed in the equation:

\[
\text{ITBV} = a \cdot \text{GEDV} + b \quad [4]
\]

where a specific coefficient \( a = 1.16 \) and a specific constant \( b = 86 \text{ mL/m}^2 \) were found for humans.

Since there is a linear relation between GEDV and ITBV, ITBV can be estimated from GEDV, and therefore EVLW can be calculated as the difference between ITTV and ITBV.

\[
\text{EVLW} = \text{ITTV} - \text{ITBV} \quad [5]
\]

\[
\text{EVLW} = \frac{\text{ITTV} - \text{ITBV}}{\text{weight}} \quad [6]
\]

Thus, calculation of EVLW can be derived with a single-indicator dilution technique. The calculations performed to obtain the value of EVLW with this technique are described in detail by Sakka et al. (6).

**Experimental Groups.** Dogs were divided into three groups: group 1, control (n = 5); group 2, oleic acid-induced increased permeability pulmonary edema (n = 5); and group 3, left atrial balloon-induced hydrostatic pulmonary edema (n = 5).

In all groups, transpulmonary thermodilution (TDtp) was measured by a triple fracture injection of 0.2 mL/kg of ice-cold saline. A set of TDtp measurements was obtained within 5 mins.

The control animals were ventilated for 2 hrs, and after the transpulmonary thermodilution measurement, intravenous heparin, 5000 units, was injected and the animals were killed using intravenous KCL solution. The chest was opened via sternotomy, the trachea and hilus were clamped, and the lungs were immediately removed. We then measured EVLWI by gravimetric method.

In group 2, baseline measurements of EVLWI were performed after a stabilization period, following which permeability pulmonary edema was induced by injection of oleic acid 0.2 mL/kg mixed with the animal’s blood over 30 mins into a central venous catheter. After appearance of frank pulmonary edema, a thermodilution EVLWI measurement was performed, following which the dogs were killed. The lungs were excised in the same manner as the control group for gravimetric analysis.

In group 3, after a stabilization period, the chest was opened via sternotomy and an 18-Fr Foley catheter was introduced into the left atrium through a purse string suture. The chest was closed, and the animals were allowed to stabilize. After stabilization, the Foley catheter balloon was inflated with 15–20 mL of fluid to achieve PAOP >25 mm Hg. An infusion of lactated Ringer’s solution was used to maintain PAOP at a constant level >25 mm Hg. The animals were maintained in this manner for 2 hrs. A transpulmonary thermodilution was then performed, the animals were killed, and gravimetric analysis of the lungs was performed as in the other two groups.

We also compared the ratio between EVLWI and ITBV as an indicator of permeability in all three groups.

**Statistical Analysis.** Absolute values for EVLWI were indexed for body weight. Other hemodynamic measurements were indexed for body surface area.

Because of the size of the groups and the asymmetric distribution of the EVLWI values, nonparametric statistical models were used. EVLWI measured by the gravimetric method was compared with the single-indicator dilution method using the Spearman correlation. Intergroup comparison for each of the methods used was done using the Kruskal-Wallis test.

Since the gravimetric method to measure EVLWI is a true gold standard, we did not use Bland-Altman analysis. As Bland and Altman note in their publication, their analysis is designed for comparing two clinical methods neither of which is considered to be a true gold standard.

We considered \( p < .05 \) to be significant. All values are given as mean ± SD.

**RESULTS**

The baseline thermodilution EVLWI was 9.12 ± 2.2 mL/kg in all dogs. Overall, we observed a very close (\( r = .967, p < .001 \)) correlation between the EVLWI measurements evaluated by transpulmonary thermodilution and gravimetry.

Average cardiac output for all three groups was 3.87 ± 1.1 L/min. It did not change for the control group. In group 2 (oleic acid), the cardiac output before the animals were killed was 1.5 ± 0.17 L/min, and in group 3 (left atrial balloon), the cardiac output was 2.8 ± 1.3 L/min before the animals were killed.

The EVLWI in group 1 (control) was 9.4 ± 3.5 mL/kg with the PiCCO and 7.08
common crease in EVLWI is the pathophysiologic demonstration previously with single-indicator dilution measurements of EVLWI. Such a relationship was not demonstrated with the transpulmonary thermodilution method. In group 1 (control; Fig. 2). The intrathoracic blood volume is a preload variable indicating the left ventricular end diastolic volume. The ratio between EVLW and the degree of preload was examined to assess its utility as a marker of permeability.

The increase in EVLW/ITBV ratio was not due solely to the increased accumulation in EVLW, as can be seen in Figure 3. In the group with left atrial balloon, even when a large quantity of EVLW was accumulated, a high preload state was required, thus maintaining the ratio at a lower value than in the group 2 animals in which a high EVLW was measured at low preload values.

**DISCUSSION**

Our results show that EVLWI measurements with the transpulmonary thermodilution method are closely related to the gold standard gravimetric technique. This is true in both high-pressure and increased permeability pulmonary edema. Such a relationship was not demonstrated previously with single-indicator dilution measurements of EVLWI.

**Clinical Significance of EVLWI.** An increase in EVLWI is the pathophysiological basis for the development of PE, a common finding in many critically ill patients that may also occur during surgery. The early recognition and differential diagnosis of hydrostatic and increased permeability PE may be challenging, since most common manifestations of PE such as dyspnea, markedly reduced lung compliance, and hypoxemia are nonspecific and usually late signs of PE. Clinical and radiologic signs of PE often do not appear until EVLWI doubles or triples (9). The chest roentgenogram is the most frequently used method for diagnosis of PE. However, technical difficulties, such as quality of roentgenograms obtained at routine bedside conditions, position of the patient, lung volume, and the presence of other radiographic abnormalities (pleural effusion, chronic obstructive pulmonary disease), may explain the variability of individual interpretations (2, 10). A more accurate assessment of PE can be achieved by computed tomography scanning (11). However, computed tomography is not available at the bedside, and the information provided is limited to one point in time. Other methods, such as positron emission tomography scan or nuclear resonance imaging, can only be used as research tools (12).

The only clinical technique for EVLWI measurement has been the use of double-indicator (thermo-dye) dilution. This technique has been validated against gravimetric measurement of EVLWI and has been demonstrated to be a useful clinical tool for the management of patients with lung injury (1, 13). Eisenberg et al. (13) demonstrated the utility of EVLWI measurement at the bedside for management of critically ill patients and showed that using EVLWI measurements for clinical decisions hastens resolution of pulmonary edema and may improve outcome in some critically ill patients. Mitchell et al. (1) showed that using EVLWI measurement to manage the fluid administration in patients in the intensive care unit can significantly reduce fluid administration, ventilator days, and intensive care unit duration.

EVLWI has also been described as a tool to help titrate and predict the response of critically ill patients to different ventilatory modes (14, 15).

**Technique of Single Indicator Thermodilution.** Our findings are quite consistent with previous reports using the double-indicator dilution as the reference technique.

In 40 critically ill patients, Baudendistel et al. (16) showed that single-indicator dilution can identify and quantify the early phases of EVLWI accumulation in patients with ARDS.

Schuster and Calandrino (17) found significant discrepancies between the two techniques in 18 critically ill patients. However, this finding was explained by technical factors related to catheter design that cannot be applied to the technique described in our study using the PiCCO. Schuster and Calandrino (17) detailed the problems in the technique and measurement of extravascular lung water using transpulmonary thermodilution with a single indicator is very closely correlated with gravimetric measurement of lung water in both increased permeability and hydrostatic pulmonary edema.
In patients with cardiogenic pulmonary mechanism leading to pulmonary edema.

EVLWI (Extravascular Lung Water Index) is a measure used to quantify the amount of fluid in the interstitial space of the lungs. It is an important variable for diagnosis and treatment of pulmonary edema.

**Correlation of extravascular lung water**

**Figure 4.** Correlation of extravascular lung water index (EVLWI) measured by PiCCO compared with gravimetric measurement.

**EVLW/ITBV Ratio.** The degree of increase in EVLW is influenced by the mechanism leading to pulmonary edema. In patients with cardiogenic pulmonary edema, even a large increase in preload will lead to moderate increases in EVLW. At the same time, in noncardiogenic pulmonary edema, the increment in EVLW can be substantially higher (19, 20), even at lower preload or filling pressures.

We compared the ratio of EVLW to a preload determinant, the ITBV, to assess the utility of such a ratio in differentiation of hydrostatic and increased permeability pulmonary edema. We found that the EVLWI/ITBV ratio was highest in the dogs with oleic acid-induced lung injury, $1.64 \pm 0.38$. The ratio was significantly lower in the group with hydrostatic pulmonary edema, $0.80 \pm 0.16$. The ratio was $0.37 \pm 0.12$ in the control group. The difference between all three groups was highly significant ($p = .002$).

One outlier animal in the cardiogenic pulmonary edema group accumulated a large amount of EVLW; however, this was associated with a very high preload state, ITBV, so that the ratio of EVLW to ITBV was maintained at 1.04 even in this instance.

Thus, the ratio between EVLW and ITBV did indeed separate increased permeability from hydrostatic pulmonary edema and should be considered an additional diagnostic tool for this purpose. In many cases in which the etiology of pulmonary edema is unclear, a variable indicating the degree of permeability could be helpful in diagnosing and directing therapy.

**Limitations of the Study.** EVLWI measured by the PiCCO showed a slight consistent overestimation compared with the gravimetric method. This is due to a number of reasons. The thermal indicator equilibrates with myocardium and vessel walls, thus leading to a small increase in the EVLWI measured.

An additional cause for this discrepancy may be related to calculation of ITBV and EVLWI. Using single-indicator dilution, ITBV and EVLWI were derived from the measured cardiac output, ITTV, and PTV. This requires use of an equation that uses coefficients derived from animal and patient models (6, 21, 22). In fact, the PiCCO system uses coefficients that are appropriate for human use, and the fact that our model is a dog model may have influenced the measurements to some degree.

Despite these limitations, the apparent slight overestimation of EVLWI with the PiCCO system is not a real limitation of the system for clinical use, because of both the small difference between the two techniques and the fact that this difference is quite consistent with a difference of $3.01 \pm 1.34 \text{mL/kg}$.

Because we used a gravimetric method to measure lung water, we could only obtain one pair of measurements to compare gravimetric measurement to the thermodilution measurement. Although we could not compare the measurements over a time course, the high correlation between the two measurements does suggest that the thermodilution method provides a value that is very close to the gravimetric method, in normal subjects, as well as in pulmonary edema due to a hydrostatic etiology or due to increased permeability.

**CONCLUSIONS**

We compared EVLWI measurements by transpulmonary thermodilution and the reference gravimetric method. The EVLWI values that were measured by transpulmonary thermodilution in dogs with normal and edematous lungs correlated very closely with the gravimetric technique. This finding proves that single-indicator technique is a reliable tool for determination EVLWI.

Since EVLWI is an important variable for diagnosis and treatment of pulmonary edema and may be very helpful for guiding fluid therapy in the critically ill, the validity of this measurement using a simple bedside tool may have significant impact on management of patients with pulmonary edema.

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**REFERENCES**


